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**W-8060 Dachau(DE)**(54) **N-Acyl-2,3-benzodiazepine derivatives, pharmaceutical compositions containing them and process for preparing same.**

(57) The invention relates to novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I), their stereoisomers and acid-addition salts, pharmaceutical compositions containing them and a process for their preparation. In the general formula (I)

- R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or
- R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;
- R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;
- R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

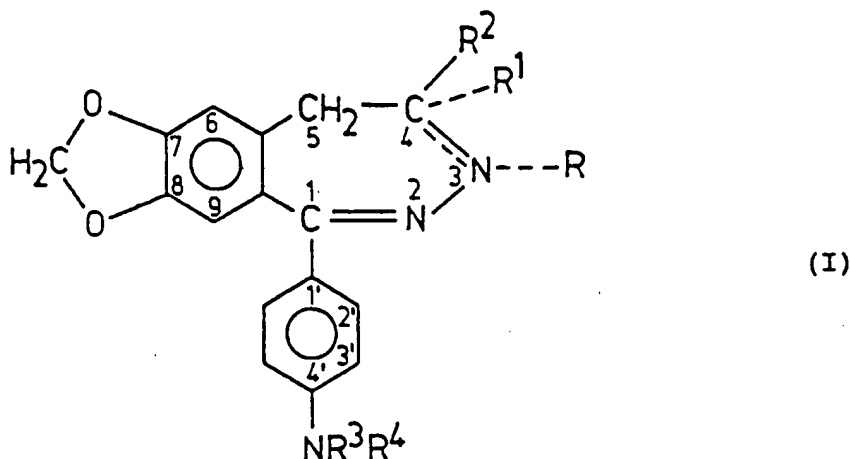
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the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen.

The compounds of the general formula (I) possess valuable central nervous system effects, particularly muscle-relaxant, anticonvulsive and neuroprotective action. Thus, they may be useful for the treatment of various diseases of central nervous system origin.

This invention relates to novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I)



wherein

R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or

R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;

R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen,

and their stereoisomers as well as acid addition salts (where possible) and pharmaceutical compositions containing these compounds.

As number of carbon atoms in the respective groups 1 to 4 (so far as not anyhow the upper limit is 4), particularly 1 or 2, is preferred. From the halogen atoms fluorine and chlorine are preferred. In case of fluorine atoms preferably 3 of them are present as substituents.

The compounds of general formula (I) according to the invention have an asymmetric molecular structure. The general formula (I) relates to all possible individual stereoisomers and their mixtures.

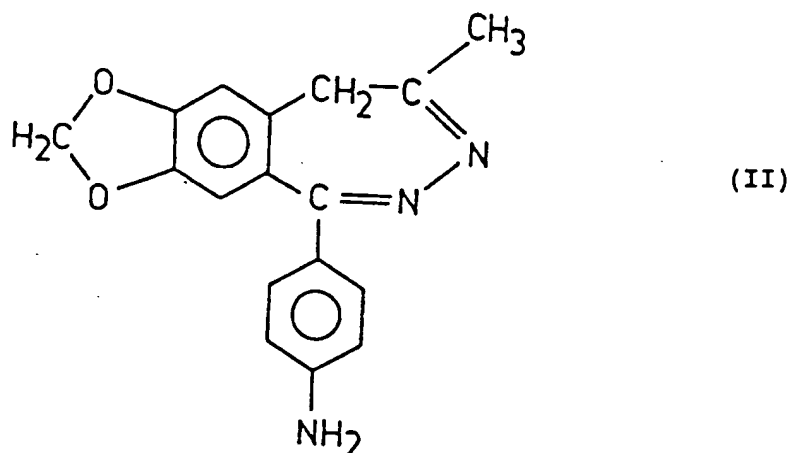
According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I) and the acid-addition salts thereof.

The aim of the present invention is to develop new compounds of the general formula (I) which possess valuable central nervous system (CNS), particularly muscle-relaxant and/or anticonvulsive, activity. A single compound showing such effect is only known among 2,3-benzodiazepines, namely 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (United States patent specification No. 4,614,740) also prepared by the authors of the present invention. In the course of detailed pharmacological screening it was revealed, however, that the above compound was positive in the Ames-test, i.e. it proved to be mutagenic. Thus, it is the specific aim of the present invention to find out novel 2,3-benzodiazepine derivatives which retain their valuable muscle-relaxant and anticonvulsive activity but are negative in the Ames test.

The new compounds of general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined above, and their pharmaceutically acceptable acid-addition salts completely satisfy this requirement.

According to the invention, the compounds of general formula (I) are prepared by

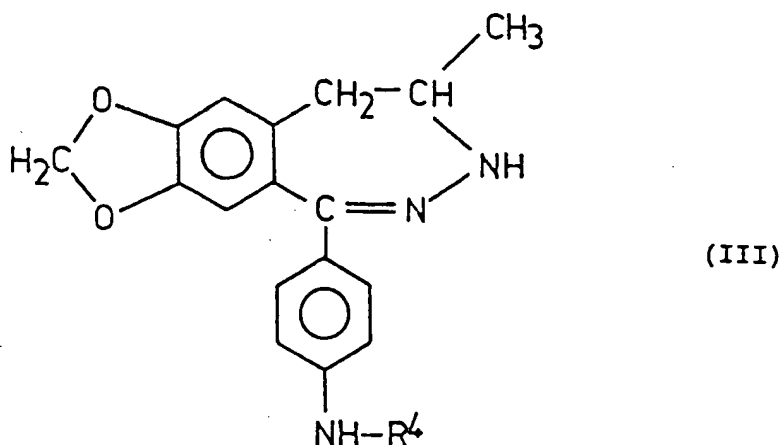
a) acylating a compound of formula (II)



with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine,

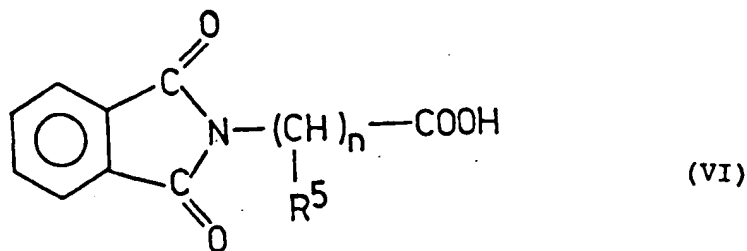
to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

b) acylating a compound of the general formula (III),



wherein R<sup>4</sup> is as defined above, with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined above, R means a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



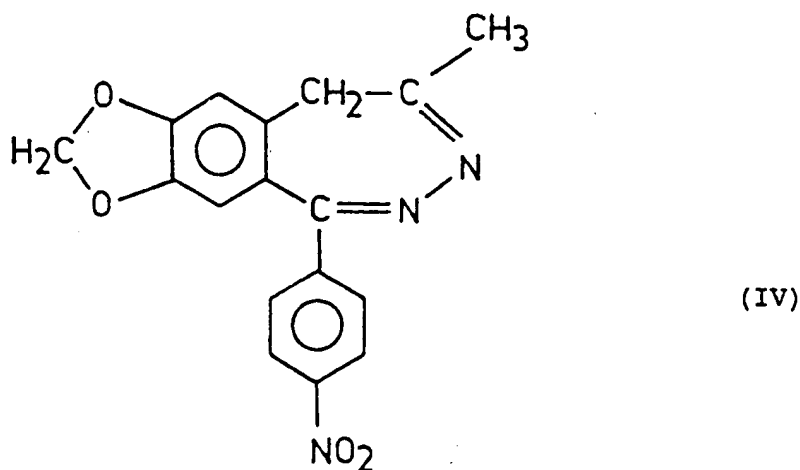
10 wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> stands for a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group, both R and R<sup>1</sup> are absent, and a double bond is present between the N(3) and C(4) atoms; or

15 d) acylating a compound of the general formula (III), wherein R<sup>4</sup> is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> is as defined above except hydrogen, R stands for a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

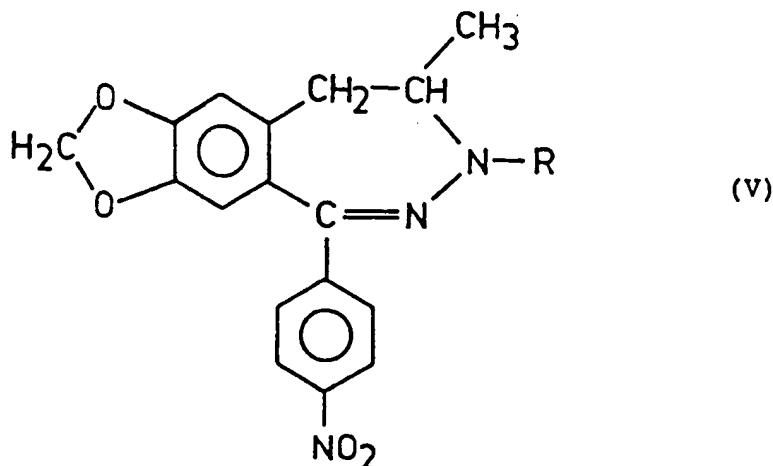
20 e) reacting a compound of the formula (II) with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group, R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms; or

25 f) reacting a compound of the general formula (III), wherein R<sup>4</sup> is defined as above, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> is as defined above except hydrogen, R stands for a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

30 g) selectively reducing a nitro compound of the formula (IV)



55 to a novel compound of the general formula (V)



wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R<sup>4</sup> stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> represent hydrogen, R<sup>2</sup>, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R and R<sup>4</sup> represent a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen; R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R represents a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen, R<sup>4</sup> represents a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

According to a preferred embodiment of the process of the present invention the acylation of the compounds of the general formulae (I), (II), (III) and (V) can be carried out preferably with a suitable carboxylic acid, in the presence of dicyclohexyl-carbodiimide in a suitable solvent, preferably in dichloromethane, in a temperature range of 10 to 30 °C during 1 to 25 hours.

According to an other preferred embodiment of the present invention the compounds of the general formulae (I), (II), (III) and (V) can be acylated in a temperature range of zero to 150 °C by a suitable

reactive acyl derivative, i.e. carboxylic acid anhydride, mixed anhydride or acyl chloride, in the absence or presence of a solvent usually applied in acylations of such types such as chloroform or dichloromethane, in the absence or presence of an acid-binding agent, such as triethylamine. If the additive acylation is performed with isocyanates, the reaction is advantageously carried out in dimethylformamide, benzene or dichloromethane in a temperature range of 15 to 100 °C during 0.5 to 100 hours.

The selective reduction of the compound of general formula (IV) to the compound of general formula (V), wherein R denotes a hydrogen atom, can be performed by an inorganic or inorganic-organic complex metal hydride, preferably sodium borohydride, in a solvent or solvent mixture which has no or only low reactivity to the complex metal hydride applied. In these reactions a C<sub>1-4</sub> alcohol or pyridine is the solvent of choice. (Similar selective reductions are described in the U.S. patent specifications Nos. 4,423,044 and 4,835,152.)

The nitro group of the new compounds of general formula (V) are reduced to an amino group by hydrazine or hydrazine hydrate in the presence of a catalyst such as palladium, platinum or Raney nickel in a C<sub>1-4</sub> alcohol, dioxane, tetrahydrofuran, benzene, dimethylformamide, dimethylacetamide or in a mixture thereof.

According to a preferred embodiment of the process of the present invention the reduction can be carried out in methanol by hydrazine or hydrazine hydrate in the presence of Raney nickel catalyst in a temperature range of 10 to 65 °C (U.S. patent specification No. 4,614,740) but, if desired, the reduction and the removal of the phthaloyl protecting group described in process d) can be performed in the same vessel.

The N-phthaloylamino acids of the general formula (IV) containing a chiral carbon atom, wherein R<sup>5</sup> means a C<sub>1-4</sub> alkyl group and n is 1, can be prepared from DL-, L- and/or D-alpha-amino acids.

The compounds of the general formula (I) of the invention, which contain a basic amino group, wherein R<sup>3</sup> and R<sup>4</sup> mean a hydrogen atom or R and/or R<sup>4</sup> stand for an aminoacyl group, can be transformed to their acid-addition salts by known methods.

The preparation of the compounds of the general formula (II) used as starting materials in the process of the present invention is described in the U. S. patent specification No. 4,614,740, that of the compound of the general formula (III), wherein R<sup>4</sup> stands for a hydrogen atom, in the U. S. patent specification No. 4,835,152, while that of the compound of general formula (IV) is published in the French patent specification No. 85,09793. The compounds of general formula (III), wherein R<sup>4</sup> stands for various acyl groups, are new.

The process for their preparation is described hereinafter, before Table 10, or they can be synthesized by methods described therein. The preparation of the new starting compounds of the general formula (V) is described in the Examples. The (α-ε)-amino acid derivatives of general formula (VI) are prepared by methods known from the literature [J. Am. Chem. Soc. 35, 1133 (1913); 41, 845 (1919); Berichte der Deutschen Chemischen Gesellschaft 40, 498, 2649 (1907); 46, 1103, 3159 (1913); 47, 3166 (1914)] or by known methods using the reaction of phthalimide potassium with the required halocarboxylic acid.

The compounds of the general formula (I) prepared by the process of the present invention possess central nervous system (CNS) activity, such as anticonvulsive, muscle-relaxant and neuroprotective effects, which can be shown by pharmacological tests.

In the comparative study 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (U. S. patent specification No. 4,614,740, in the following "reference compound"), having similar structure and efficacy as the compounds of the invention, was applied as reference compound. As already mentioned in the introduction, this compound proved to be Ames-positive in addition to its valuable pharmacological properties. In opposition to this the compounds of the present invention proved to be negative in the Ames-test.

The pharmacological effects of the compounds of general formula (I) are presented in Tables 1 to 8.

#### Narcosis-potentiating effect in mice

The narcosis-potentiating effect was tested with 3 oral doses in 10 mice/dose. The ED<sub>50</sub> value is the dose prolonging the narcosis period induced by 50 mg/kg of i.v. sodium hexobarbital to its twofold value in 50 % of the animals in comparison to the control group treated only with the vehicle. The ED<sub>50</sub> values were calculated by the Litchfield-Wilcoxon method [J. Pharmacol. Exp. Ther. 96, 99 (1949)]. The results are presented in Table 1.

Tabl 1

## Narcosis potentiating effect in mice

Compound	ED <sub>50</sub> p.o.
<u>Example No.</u>	<u>mg/kg</u>
Reference compound	7.4
15 (16)	3.6
18	8.8
39	27.5
42	7.9
44	13.5

Table 1 (contd.)

Compound	ED <sub>50</sub> p.o.
<u>Example No.</u>	<u>mg/kg</u>
44	13.5
45	4.9
46	11.5
48	5-8
49	9.5
56	12.5-25
60	4.4
62	5.2
66	24.0
69	15-20
73	4.5
98	5.8
107	6.25-12.5
108	≈ 12.5
109	≈ 12.5
115	7.7

The data of Table 1 demonstrate that the efficacy of several compounds is similar or significantly superior to that of the reference compound. Compounds of Examples 15 (16), 45, 60, 73 and 98 proved to



be especially potent.

#### Anticonvulsive effect in mice

The anticonvulsive effect of the compounds was measured by using the electroshock test [Swinyard: J. Pharmacol. Exp. Ther. 106, 319 (1952)], furthermore by using various chemical agents such as pentetrazole [Goodman: J. Pharmacol. Exp. Ther. 108, 168 (1953)], strychnine [Roskovski: J. Pharmacol. Exp. Ther. 129, 75 (1960)], bemegride, nicotine and 4-aminopyridine. The test compounds were orally administered in 3 doses, to 10 male CFLP mice per dose.

The results are presented in Table 2.

Table 2

#### Anticonvulsive effect in mice

Compound	ES	Pentetr-	Strychnine	Bemegride	Nicotine	4-AP
Example No.		azole	ED <sub>50</sub> p.o.			
			mg/kg			
Reference compound	38	115	87	73	70	43
15 (16)	12.5	37	>200	16	45	9
18	17.5	29				
39	53	170	>200	>200	>200	29
42	24	33	28	24	155	34
45	27	44	>100	51	30-80	≈70
46	20	57	>100	70-80	≈100	25-30
48	10.5	35-40				
49	25	53	>100	30-35	45	28
60	24	62				
62	12.5	56		25-50		
66	42	135	≈100	>100	100-150	84
69	57	>100				
73	16	62	50-100	49	53	25
98	8.4	19	20	11	19	13.5
107	23.5	120				
108	27	>100				
109	21	>100				
115	17.1	23.9				

ES = electroshock    4-AP = 4-aminopyridine

The above data demonstrate that the anticonvulsive effect of several test compounds (of Examples 15, 42, 45, 46, 73, 98, 107, 108, 109 and 115) is superior to that of the reference compound.

#### Muscle-relaxant activity in mice

The muscle-relaxant activity was measured in two tests. In Randall's inclined screen test [J. Pharmacol. Exp. Ther. 129, 163 (1960)] the compounds were applied in 3 i.p. doses to 10 CFLP mice per dose. The results are shown in Table 3.

**Table 3**  
**Inclined screen test in mice**

Compound	ED <sub>50</sub> i.p.
<u>Example No.</u>	<u>mg/kg</u>
Reference compound	47
15 (16)	23.5
18	31
42	42
45	35
48	20.5
49	36
60	150
62	25
66	52
73	27
98	18.0
107	>200
108	>200
109	61
<u>115</u>	<u>16.1</u>

The rotarod test was used to measure muscular tone and motor coordination [Dunham and Miya: J. Am. Pharm. Assoc. 46, 208 (1957)]. The results obtained with the three selected compounds of highest activity and that of the reference compound are presented in Table 4.

**Table 4**  
**Rotarod test in mice**

Compound	ED <sub>50</sub> i.p.
<u>Example No.</u>	<u>mg/kg</u>
Reference compound	24
15 (16)	3.7
42	8.1
98	8.6

Tables 3 and 4 demonstrate that several compounds possess strong muscle-relaxant activity (compounds of Examples 15, 18, 42, 45, 48, 49, 62, 73, 98 and 115).

#### Effect on spinal function

The effect on spinal function was studied with the most active compound (compound of Example 15 or 16) and the reference compound. Table 5 shows the effect on polysynaptic flexor reflexes in cats [Farkas and Kárpáti: Pharm. Res. Comm. 20, S1, 141 (1988)].

Table 5

Effect on spinal flexor reflex			
Compound Example No.	Cumulative doses mg/kg, i.v.	Inhibition of flexor reflex in per cent of control	ED <sub>50</sub> mg/kg
Reference compound	0.25	12	0.90 (0.46-1.76)
	0.5	30	
	1.0	57	
	2.0	77	
15 (16)	0.05	11	(0.19-0.62)
	0.1	19	
	0.2	31	
	0.4	52	
	0.8	77	

The effect of the above compounds on the spinal root potentials in cats was tested in spinally immobilized animals [Farkas et al.: Neuropharmacology 21, 161 (1989)].

The results are presented in Table 6.

Table 6

Effect on spinal root potentials in cats					
Compound Example No.	Inhibition of reflexes in per cent of control				
	Cumulative i.v. doses mg/kg	Monosynaptic reflex	Polysynaptic reflex	Dorsal root reflex	Dorsal root potential
Reference compound	0.5	16	15	0	2
	1.0	27	24	2	4
	2.0	47	43	4	4
15 (16)	0.1	10	8	1	1
	0.2	10	16	3	2
	0.4	32	29	5	4
	0.8	56	51	11	8
	1.4	78	73	14	14

Monosynaptic reflex-inhibiting ED<sub>50</sub> values:

Reference compound: 2.20 (1.02-4.75) mg/kg, i.v.

Compound No. 15 (16): 2.30 (1.06-5.01) mg/kg, i.v.

Polysynaptic reflex-inhibiting ED<sub>50</sub> values:

Reference compound: 0.60 (0.32-1.13) mg/kg, i.v.

Compound No. 15 (16): 0.73 (0.39-1.37) mg/kg, i.v.

#### Electrophysiological tests

The inhibitory effects on the field potentials induced by electric stimulation in surviving rat neocortex slices in vitro [Fletcher et al., Br. J. Pharmacology 95, 585 (1988)] are summarized in Table 7.

Table 7

Inhibition of field potentials induced in rat neocortex slices			
Compound Example No.	Concentration $\mu$ M	Inhibition of induced field potentials in % of control	IC <sub>50</sub> $\mu$ M
Reference compound	10	22	30.0
	20	39	
	40	62	
	80	73	
15 (16)	10	30	21.5
	20	47	
	40	69	
	80	82	

The non-NMDA (quisqualate) antagonist effect was tested in rat neocortex slices by using the method of Harrison and Simmonds [Br. J. Pharmacol. 84, 381 (1981)]. In rat neocortex slices the DC-potential changes induced by quisqualate perfusion were dose-dependently inhibited by the reference compound in the concentration range of 10-50  $\mu$ M. At the concentration defined, the compound of Example 15 (16) proved to be twice as active as the reference compound in inhibiting the response to the 2-minute perfusion with 10  $\mu$ M of quisqualate. However, both molecules failed to affect the responses induced by NMDA. Accordingly, the compound of Example 15 (16) can be considered to be a selective, non-NMDA but quisqualate-type excitatory amino acid antagonist.

#### Acute toxicity in rats

Acute toxicity data obtained in rats are summarized in Table 8.

Table 8

Acute toxicity in rats			
Compound Example No.	Sex	Route of administration	LD <sub>50</sub> mg/kg
15 (16)	Male	i.p.	145 (128-163.1)
	Male	p.o.	≈200
	Female	i.p.	140 (122-161)
	Female	p.o.	235 (190-291)
42	Male	i.p.	155 (109.9-218.5)
	Male	p.o.	>600
	Female	i.p.	180 (156.5-207.0)
	Female	p.o.	>600

At toxic dose levels the compounds induced a dose-dependent muscle tone reduction, ataxia, adynamia, and loss of the righting reflex. The cause of mortality was respiratory insufficiency developing within 1 to 2 hours after i.p. administration and within 10 to 20 hours after oral application.

Based on the above pharmacological results, the compounds of general formula (I) according to the invention possess significant anticonvulsive, muscle-relaxant and excitatory amino acid-antagonist (neuroprotective) effects. Thus, they are therapeutically useful for the treatment of epilepsy as well as various diseases connected with spasms of the skeletal musculature and cerebral ischaemia (stroke).

The invention also relates to pharmaceutical compositions containing compounds of general formula (I) or pharmaceutically acceptable acid-addition salts thereof as active ingredients as well as to the preparation of these compositions.

For therapeutical use, the active compounds according to the invention are suitably formulated to pharmaceutical compositions by admixing them with commonly used nontoxic, inert, solid or liquid pharmaceutical carriers and/or auxiliary materials useful for enteral or parenteral administration. As carriers, e.g. water, gelatine, lactose, starch, pectin, magnesium stearate, stearic acid, talc or vegetable oils can be used. As auxiliary materials, e.g. preservatives and wetting as well as emulsifying, dispersing and aromatizing agents and buffers can be employed.

By using the above-mentioned carriers and auxiliary materials, the active agents of the invention may be transformed to the usual pharmaceutical compositions, e.g. to solid compositions (such as tablets, capsules, pills or suppositories) or liquid compositions (such as aqueous or oily solutions, suspensions, emulsions or syrups) as well as to injectable solutions, suspensions or emulsions.

For therapeutical purposes, the daily dose of the compounds of the invention amounts commonly to 0.2-1.5 mg/kg of body weight which is administered daily, optionally divided to several doses.

Based on the above facts, the present invention also provides:

- a method of blocking one or more excitatory amino acid receptors in mammals. This method comprises administering to a mammal in need of such treatment a pharmaceutically effective amount of the general formula (I);
- a method of treating epilepsy in mammals. This method comprises administering to the mammal in need of such treatment an antiepileptic amount of a compound of the general formula (I);
- a method of treating spasms of the skeletal musculature in mammals. This method comprises administering to the mammal in need of such treatment a muscle-relaxing amount of a compound of the general formula (I);
- a method of treating cerebral ischaemia (stroke) in mammals. This method comprises administering to the mammal in need of such treatment a pharmaceutically effective amount of a compound of the general formula (I).

The compounds prepared by the process of the invention were identified by elementary analysis, their purity and structure were controlled and confirmed by thin-layer chromatography, IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and mass spectrometry.

The invention is illustrated in detail by the following non-limiting Examples.

#### Exempl 1

**1-(4-Diacetylaminophenyl)-3-aminophenyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

2.93 g (0.01 mol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were refluxed with 20 ml of acetic anhydride for 6 hours. The solution was evaporated at reduced pressure, the residue was taken up in 2x20 ml of anhydrous ethanol, the solution was repeatedly evaporated and the resulting residue of 4.55 g was submitted to column chromatography (adsorbent: Kieselgel 60, eluant: ethyl acetate - benzene 4:1). The raw product was triturated with 20 ml of hot isopropanol to yield 1.44 g (34.4 %) of the aimed product, m.p. 240-245 °C (slight decomp.).

$C_{23}H_{21}N_3O_5 = 419.445$

**Example 2**

**1-(4-Formylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

3.0 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were dissolved in 160 ml of dichloromethane and first 2.75 g (13.3 mmol) of dicyclohexylcarbodiimide, then 0.51 ml (13.3 mmol) of 100 % formic acid were added and the reaction mixture was stirred for 2 hours at room temperature. The precipitated N,N'-dicyclohexylurea was filtered, the filtrate was extracted with 2x30 ml of 10 % aqueous sodium carbonate solution, then with 2x30 ml of distilled water, the organic layer was dried and evaporated at reduced pressure. The residue was dissolved in ethyl acetate, filtered and evaporated under reduced pressure. The resulting raw product was recrystallized from 20 ml of 50 % ethanol to yield 2.93 g (89.3 %) of the aimed product, m.p. 152-154 °C (slight decomp.).

$C_{18}H_{15}N_3O_3 = 321.342$

**Examples 3 to 7**

The compounds of Examples 3 to 7 were prepared by the process described in Example 2.

**Example 3**

**1-(4-Cyanoacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine**

$C_{20}H_{16}N_4O_3 = 360.380$ , m.p.: 241-243 °C (decomp.).

**Example 4**

**1-(4-Methoxyacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine**

$C_{20}H_{19}N_3O_4 = 365.396$ , m.p.: 203-205 °C

**Example 5**

**1-(4-Valerylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

$C_{22}H_{23}N_3O_3 = 377.450$ , m.p.: 217-219 °C (decomp.).

**Example 6**

**1-(4-Phenylacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine**

$C_{25}H_{21}N_3O_3 = 411.467$ , m.p.: 245-247 °C (decomp.).

**Example 7**

**1-(4-Cyclopropylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

$C_{21}H_{19}N_3O_3 = 361.407$ , m.p.: 260-262 °C (decomp.).

**Exempl 8****1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

10 g (34 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were stirred for 3 hours with 100 ml of acetic anhydride. The crystals formed were filtered, washed with 5x10 ml of anhydrous ethanol and dried, yielding 9.2 g of raw product, m.p. 252-254 °C (decomp.). This product was treated with 45 ml of hot 99.5 % ethanol. After cooling the crystals were filtered, washed with 3x10 ml of ethanol and dried to give 8.68 g (76.1 %) of the aimed product, m.p.: 256-258 °C (decomp.).

$C_{19}H_{17}N_3O_3 = 335.369$

**Example 9****1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

$C_{20}H_{19}N_3O_3 = 349.396$ , m.p.: 228-230 °C (decomp.).

It was prepared by the process described in Example 8.

**Example 10****1-(4-Pivaloylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

1.56 ml (11.2 mmol) of triethylamine and 1.38 ml (11.2 mmol) of pivaloyl chloride were added to a solution of 3 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 160 ml of dichloromethane and the reaction mixture was stirred at 25 °C for one hour. The precipitate formed was filtered, washed with 3x5 ml of dichloromethane, then with 3x20 ml of water and dried to yield 1.59 g of pure product, m.p. 225-227 °C (decomp.). The other portion of the product was isolated from the organic phase. The filtrate was extracted with 3x20 ml of water, then with 3x15 ml of 4 % aqueous sodium hydroxide solution, finally with 2x30 ml of water. The organic layer was subsequently dried and evaporated under reduced pressure. The crystalline residue was combined with the former product of 1.59 g and suspended in 20 ml of hot ethanol. The product was filtered after cooling, washed with 3x3 ml of ethanol and dried to yield 3.38 g (87.8 %) of the pure product, m.p.: 225-227 °C (decomp.).

$C_{22}H_{23}N_3O_3 = 377.450$

**Example 11****1-(4-Benzoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

1.0 ml (15 mmol) of benzoyl chloride and 2.1 ml (15 mmol) of triethylamine were added to a solution of 4 g (13.6 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane and the reaction mixture was stirred at 25 °C for 24 hours. The solution was extracted with 3x30 ml of water, 3x20 ml of a 4 % aqueous sodium hydroxide solution and finally with 2x30 ml of distilled water. The organic layer was dried, evaporated under reduced pressure, then the crystalline residue was treated with 20 ml of hot ethanol to obtain 3.97 g of raw product, m.p. 242-243 °C. This raw product was repeatedly treated with 20 ml of hot ethanol, next day it was filtered at 0-5 °C, washed with 3x3 ml of ethanol and dried at 100 °C to yield 3.85 g (71.3 %) of the pure aimed product, m.p. 246--247 °C (decomp.).

$C_{24}H_{19}N_3O_3 = 397.40$

**Example 12****1-(4-Palmitoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

By following the process described in Example 11, with recrystallization of the raw product from 50 % ethanol, the pure aimed product was obtained, m.p. 138-140 °C.

$C_{33}H_{45}N_3O_3 = 531.747$

**Example 13**

**1-(4-Phenylcarbamylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

0.22 ml (2.04 mmol) of phenyl isocyanate was added to a solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 4 ml of dimethylformamide and the reaction mixture was stirred at 25 °C for one hour. Then it was diluted with 20 ml of diethyl ether and filtered at 5 °C. The crystals were washed with 2x5 ml of diethyl ether and dried at 60-100 °C. The resulting 0.70 g of raw product, m.p. 239-240 °C (sintering at 180 °C) was refluxed in 15 ml of ethanol, filtered after cooling, washed with 3x1 ml of ethanol and dried at 100 °C to yield 0.55 g (78.6 %) of the aimed product, m.p. 240-241 °C (decomp.).

$C_{24}H_{20}N_4O_3 = 412.456$

**Example 14****1-[4-(4-Carboxybutylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

A solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 30 ml of anhydrous dichloromethane was stirred with 0.18 g (1.87 mmol) of glutaric acid anhydride at 20-25 °C for 6 hours. Next day the crystals formed were filtered at 0-5 °C, washed with 3x2 ml of dichloromethane and dried at 60-80 °C to give 0.60 g (87.0 %) of the pure aimed product, m.p. 225-227 °C (decomp.).

$C_{22}H_{21}N_3O_5 = 407.434$

**Example 15****1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

To a solution of 3.58 g (12.1 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 100 ml of chloroform first 1.68 ml (12.1 mmol) of triethylamine, then under constant ice-cooling and stirring 1.15 ml (12.1 mmol) of acetic anhydride were added. Stirring was continued for additional 2 hours, then the solution was extracted with 3x100 ml of water, the organic layer was dried and evaporated under reduced pressure. The crystalline residue was recrystallized from 40 ml of isopropanol to obtain 3.50 g (85.7 %) of the aimed product, m.p. 220-222 °C. After repeated recrystallization the m.p. increased to 223-225 °C.

$C_{19}H_{19}N_3O_3 = 337.385$

Hydrochloride:  $(C_{19}H_{20}N_3O_3)Cl = 373.850$ , m.p.: 248-252 °C (decomp.).

**Example 16****1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine**

To a suspension of 1.91 g (5.37 mmol) of 1-(4-nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (product of Example 27) in 40 ml of methanol about 0.2 g of Raney nickel catalyst and 1.4 ml (28 mmol) of 100 % hydrazine hydrate were added, then the reaction mixture was stirred at 20-25 °C for one hour. The starting nitro derivative was dissolved within 10-20 minutes. After filtering the filtrate was evaporated under reduced pressure, the white crystalline residue was washed with 30 ml of distilled water onto a filter, it was washed with 3x10 ml of distilled water and dried at 100 °C to give 1.50 g of a raw product, m.p. 218-220 °C. This raw product was purified by treating with 12 ml of hot isopropanol. After cooling it was filtered at 5 °C, washed with 3x1 ml of isopropanol and dried at 100 °C to yield 1.40 g (77.35 %) of a white crystalline powder, m.p. 221-223 °C. On the basis of analyses and spectra it was identical to the product of Example 15 obtained by a different process.

**Example 17 t 25**

The process described in Example 16 was followed for preparing other 1-(4-aminophenyl)-3-R-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepines of the general formula (I). The data of the products prepared are presented in Table 9.



Table 9

Products of the general formula (I) wherein $R_2 = CH_3$ and $R_1 = R_3 = R_4 = H$		
Example No.	R	M.p. °C
17	Trifluoroacetyl	215-217
18	Propionyl	211-213
19	Valeryl	178-180
20	Pivaloyl	233-235 (d)
21	Benzoyl	220-222
22	Phenylacetyl	220-221
23	Cyclopropylcarbonyl	138-140
24	Cyanoacetyl	123-126
25	Methoxyacetyl	125-127

(d) = decomposition

The new nitro compounds of the general formula (V), wherein  $R = H$  or acyl group, used in the preparation of products of Examples 16 to 25, can be prepared by processes described in Examples 26 to 36.

**Example 26****1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

To a suspension of 5.0 g (15.5 mmol) of the known 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (French patent specification No. 85,09793) in 380 ml of ethanol first 22.5 ml (0.278 mol) of concentrated hydrochloric acid were added at constant stirring whereupon a solution was formed within a few minutes, then 11.5 g (0.3 mole) of sodium borohydride were charged into the solution portionwise during 30 minutes. Stirring was continued for 15 minutes, then the orange-coloured precipitate formed was filtered and extracted on the filter with 4x30 ml of chloroform. The combined chloroform filtrate was evaporated under reduced pressure, the crystalline residue was brought to a filter with 200 ml of distilled water, then washed with 3x20 ml of distilled water and dried at 80-100 °C to yield 4.90 g (97.2 %) of the aimed product, m.p.: 162-164 °C.

 $C_{17}H_{15}N_3O_4 = 325.331$ **Example 27****1-(4-Nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

A 2.0 g (6.15 mmol) portion of the product of Example 26 was stirred with 10 ml of acetic anhydride at 25 °C for 3 hours then 50 ml of distilled water were added and the stirring was continued for one hour. The yellow precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 80-100 °C to obtain 2.6 g of raw product. After recrystallization from 10 ml of ethanol 1.94 g (85.8 %) of the aimed product were obtained, m.p.: 140-142 °C.

 $C_{19}H_{17}N_3O_5 = 367.369$ **Example 28****1-(4-Nitrophenyl)-3-trifluoroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

To a solution of a 1.5 g (4.61 mmol) portion of the product of Example 26 in 30 ml of anhydrous dichloromethane 0.75 ml (5.3 mmol) of trifluoroacetic acid anhydride and 0.75 ml (5.3 mmol) of triethylamine were added and the reaction mixture was stirred at 25 °C for 3 hours. Subsequently, the mixture was extracted with 3x20 ml of water and the organic layer was dried and evaporated under reduced pressure. The crystalline residue was treated with 15 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried at 80-100 °C to yield 1.84 g (94.85 %) of the aimed compound as a bright yellow crystalline product, m.p.: 165-167 °C (decomp.).

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$C_{19}H_{14}F_3N_3O_5 = 421.339$

### Example 29

#### 5 1-(4-Nitrophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A 1.54 g (4.7 mmol) portion of the product of Example 26 was stirred with 8 ml of propionic acid anhydride at 25 °C for 3 hours, then 30 ml of diethyl ether were added and the solution was kept at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x8 ml of diethyl ether and dried to yield 1.32 g (73.7 %) of the aimed compound as a light yellow product, m.p.: 189-190 °C.

$C_{20}H_{19}N_3O_5 = 381.396$

### Example 30

#### 15 1-(4-Nitrophenyl)-3-valeryl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of a 2.5 g (7.68 mmol) portion of the product of Example 26 in 40 ml of anhydrous dichloromethane 4.75 g (23 mmol) of dicyclohexylcarbodiimide and 2.88 g (23 mmol) of n-valeric acid were added and the reaction mixture was maintained at 25 °C under intermittent stirring for 24 hours. Then the N,N'-dicyclohexylurea formed as by-product was filtered, the filtrate was evaporated under reduced pressure, the residue was mixed with 2x40 ml of distilled water, decanted and the wet product was left to solidify under 50 ml of 50 % ethanol. The solid compound was filtered, washed with 2x10 ml of 50 % ethanol and dried at 80 °C. The raw product obtained was recrystallized from 24 ml of ethanol and the crystals were dried at 100 °C to yield 2.20 g (70 %) of the aimed product as a yellow powder, m.p.: 145-147 °C.

$C_{22}H_{23}N_3O_5 = 409.450$

### Example 31

#### 30 1-(4-Nitrophenyl)-3-pivaloyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 28 but applying pivaloyl chloride instead of trifluoroacetic acid anhydride, 1.68 g (89.4 %) of the aimed product were obtained, m.p.: 164-166 °C.

$C_{22}H_{23}N_3O_5 = 409.450$

### Example 32

#### 1-(4-Nitrophenyl)-3-benzoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 31 but using benzoyl chloride as acyl chloride, 1.72 g (86.9 %) of an ochre yellow product were obtained, m.p.: 222-224 °C (decomp.).

$C_{24}H_{19}N_3O_5 = 429.440$

### Example 33

#### 45 1-(4-Nitrophenyl)-3-phenylacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 30 but using 50 % of the calculated molar amount of dicyclohexylcarbodiimide and phenylacetic acid, a bright yellow product was obtained, m.p.: 193-195 °C.

$C_{25}H_{21}N_3O_5 = 443.467$

### Examples 34 to 36

The products of Examples 34 to 36 were obtained by following the process described in Example 33 and using the respective acid components.

### Example 34

**1-(4-Nitrophenyl)-3-cyclopropanecarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 225-228 °C (decomp.).

5  $C_{21}H_{19}N_3O_5 = 393.407$

**Example 35**

**1-(4-Nitrophenyl)-3-cyanoacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

10

M.p.: 185-188 °C

$C_{20}H_{16}N_4O_5 = 392.380$

**Example 36**

15

**1-(4-Nitrophenyl)-3-methoxyacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 187-189 °C

$C_{20}H_{19}N_3O_6 = 397.396$

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**Example 37**

**1-(4-Nitrophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

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By using the product of Example 26 as starting material and performing the acylation according to Example 14 with glutaric acid anhydride, finally recrystallizing the raw product from ethanol the pure aimed product was obtained, m.p.: 148-150 °C.

$C_{22}H_{21}N_3O_7 = 439.434$

30

**Example 38**

**1-(4-Aminophenyl)-3-phenylcarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

35

To a solution of 0.70 g (2.3 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 10 ml of anhydrous benzene 0.24 ml (2.3 mmol) of phenyl isocyanate was added and the reaction mixture was refluxed for one hour. Thereafter the solution was evaporated under reduced pressure and the amorphous residue was mixed with 20 ml of hot 50 % ethanol. The suspension was cooled to 0 °C and filtered to yield 0.76 g of a raw product, m.p. 190-200 °C. After recrystallization from 99.5% ethanol and trituration with ethyl acetate the aimed compound melts at 207-209 °C.

$C_{24}H_{22}N_4O_3 = 414.472$

40

The preparation of the starting material of this example was described in the Hungarian patent specification No. 198,494. However, the compound may also be prepared by a new method according to the process of Example 16, by using the compound of Example 26 as starting material to give excellent yields (84 %). The raw product may be recrystallized from 50 % ethanol, m.p.: 118-120 °C.

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**Example 39**

**1-(4-Diacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

50

2.0 g (6.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were refluxed with 40 ml of acetic anhydride for 3 hours, then it was evaporated to dryness under reduced pressure. The crystalline residue was transferred with 25 ml of water to a filter and washed with 5x3 ml of water. After drying 2.79 g of the raw triacetyl derivative were obtained. After washing with 20 ml of isopropanol and drying at 100 °C 2.39 g (84.6 %) of the pure aimed product were obtained, m.p. 224-227 °C.

55

$C_{23}H_{23}N_3O_5 = 421.461$

**Example 40****N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-methylurea**

5

0.70 g (2 mmol) of the product of Example 15 was dissolved in benzene dehydrated over calcium hydride, 0.3 ml (5 mmol) of methyl isocyanate was added and the reaction mixture was stirred at 50 °C for 4 hours. The crystals formed after cooling were filtered, washed with 3x3 ml of benzene, then triturated with 20 ml of hot benzene. The hot mixture was filtered, the precipitate was washed with 3x3 ml of benzene and

10

dried to give 0.65 g (79.6 %) of the aimed product, m.p.: 168-170 °C (decomp.).

$C_{21}H_{22}N_4O_4 = 394.439$

**Example 41****15 N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-phenylurea**

By following the process described in Example 40 but using phenyl isocyanate instead of methyl isocyanate, refluxing the reaction mixture for 10 hours, evaporating it under reduced pressure, then

20

suspending the residue first in 50 ml of diethyl ether and then in 15 ml of ethyl acetate, 0.69 g (75.7 %) of the aimed product was obtained, m.p.: 184-186 °C (decomp.).

$C_{26}H_{24}N_4O_4 = 456.510$

**Example 42**

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**1-(4-Acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

1.3 g (4.4 mmol) of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were stirred at 20-25 °C with 5 ml of acetic anhydride for one hour, then the yellow solution

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was poured into 100 g of ice-water and stirred until the decomposition of the excess anhydride became complete. The precipitate formed was filtered, washed with 3x10 ml of distilled water and dried to give 1.6 g of raw product. After recrystallization from 20 ml of benzene 1.50 g (89.85 %) of the aimed product were obtained, m.p.: 158-160 °C (decomp.).

$C_{21}H_{21}N_3O_4 = 379.423$

35

**Example 43****1-(4-Formylaminophenyl)-3-formyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

To 6.0 ml (0.104 mol) of acetic anhydride 3.0 ml (0.08 mol) of 100 % formic acid were added dropwise at 0 °C during 5 minutes while constant stirring. The stirring was continued at 50 °C for 15 minutes. Thereafter 1 g (3.3 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine was added to the thus-prepared mixed anhydride. The reaction mixture was stirred at 25 °C for 1.5 hours, then poured into ice-water, the precipitate formed was filtered, washed with 4x5 ml of

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distilled water and dried at 80 °C to give 0.80 g of raw product. After crystallization from 3 ml of ethyl acetate 0.65 g (56.2 %) of the aimed product was obtained, m.p.: 193-195 °C.

$C_{19}H_{17}N_3O_4 = 351.369$

**Example 44**

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**1-(4-Trifluoroacetylaminophenyl)-3-trifluoroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

1.48 g (5 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were dissolved in 30 ml of anhydrous chloroform, then 2.1 ml (15 mmol) of triethylamine and at 20-25 °C 2.12 ml (15 mmol) of trifluoroacetic anhydride were added and the reaction mixture was stirred for 2.5 hours, then extracted first with 2x30 ml of water and thereafter with 20 ml of 5 % hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, evaporated under reduced pressure and the

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amorphous residue was recrystallized from 10 ml of 70 % ethanol to give 1.41 g (57.9 %) of the aimed diacyl derivative, m.p. 177-178 °C.

$C_{21}H_{15}F_6N_3O_4 = 487.363$

#### 5 Example 45

##### 1-(4-Propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

10 The process described in Example 44 was followed, except that 11.2 mmol of both triethylamine and propionic acid anhydride were used and the crystalline residue was recrystallized first from 15 ml of 50 % ethanol, then from 11.5 ml of 99 % ethanol to give 2.48 g (60.9 %) of the aimed product, m.p.: 152-154 °C.  
 $C_{23}H_{25}N_3O_4 = 407.477$

#### 15 Examples 46 to 65

Other diacyl derivatives of the general formula (I), wherein R = acyl group,  $R^1 = R^3 = H$ ,  $R^2 = CH_3$  and  $R^4 =$  acyl group, where R and  $R^4$  are the same or different, are presented in Table 10. These compounds were prepared partly from compounds of the general formula (III), wherein  $R = R^1 = R^3 = H$  and  $R^4 =$  acyl group; and partly from new compounds of the general formula (I), wherein R = acyl group,  $R^1 = R^3 = R^4 = H$  and  $R^2 = CH_3$ , according to processes defined in the preceding examples.

The preparation of starting substances of general formula (III), wherein  $R = R^1 = R^3 = H$  and  $R^4 =$  acyl group is illustrated in detail below on the derivative bearing acetyl group as  $R^4$ :

#### 25 1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

##### Method A)

To a solution containing 6.0 g (20 mmol) 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 30 ml of ethyl acetate 1.38 ml (21 mmol) of methanesulfonic acid were added. The crystalline precipitate was filtered and washed with 5 x 5 ml of ethyl acetate. The dry weight of the product was 7.37 g, m.p.: it sintered above 190 °C and weakly decomposed at 210-212 °C. The thus-obtained methanesulfonate salt of the starting substance was acetylated as follows:

35 7.37 g of the powdered salt were suspended in 110 ml of acetic anhydride, the suspension was stirred at room temperature for 2 hours, then the crystalline precipitate was filtered, washed with 5 x 10 ml of ethyl acetate and dried to give 6.54 g of methanesulfonate salt of the target compound, m.p. 240-241 °C (with decomposition).

The base was liberated from the methanesulfonate salt of the target compound e.g. in the following way: 6.54 g of salt were dissolved in 90 ml of water, the solution was clarified by charcoal, then 3.6 g of sodium hydrogen carbonate were portionwise added to the clear solution. The precipitate was filtered, washed with 5 x 10 ml of water and dried to obtain 5.54 g of crude product. After recrystallization from 130 ml of isopropanol, 3.11 g (yield 46 %) of product were obtained, m.p.: 221-223 °C (weak decomposition), the melting point of which increased to 223-225 °C after digesting with 15 ml of hot benzene.

$C_{19}H_{19}N_3O_3 = 337.385$

45 The hydrochloride salt decomposed at 262-264 °C.

##### Method B)

After dissolving 15.0 g (44.7 mmol) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 150 ml of pyridine under mild heating, 10.2 g (0.269 mol) of sodium borohydride were added and the mixture was stirred on an oil bath at a temperature of 100 °C for 5 hours. Then the reaction mixture was cooled to about 25 °C, 150 ml of water were dropwise added under continuous stirring during 20 minutes, thereafter a mixture containing 180 ml of concentrated hydrochloric acid and 265 ml of water was added while cooling with ice-water. A yellowish suspension was formed. The precipitate was filtered, washed with 5 x 20 ml of water and dried to yield 15.2 g of salt, m.p. above 250 °C. In order to liberate the base, this salt was suspended in 150 ml of 50 % ethanol and then 5.7 g of sodium hydrogen carbonate were portionwise added while stirring. The thus-formed suspension was filtered after 30 minutes, washed successively with 3 x 10 ml of 50 % ethanol, 5 x 20 ml of water, finally with 20 ml of 50 % ethanol and

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dried to obtain 10.95 g of a crude product, m.p.: 218-220 °C (weak decomposition). After digesting this crude product with 50 ml of hot isopropanol and then with 100 ml of hot 99.5 % ethanol, 8.63 g (57.2 %) of the aimed compound were obtained, m.p.: 220-222 °C (weak decomposition).

Physical characteristics of other 1-(4-acylamino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine are as follows:

R <sup>4</sup> -Analogue	M.p. °C
Propionyl	237-239
Benzoyl	247-248 (decomp.)
Phenylacetyl	213-215 (decomp.)
Pivaloyl	132-135 (decomp.)

Table 10  
Compounds of the general formula (I), wherein  $R^1 = R^3 = R$ ,  $R^2 = CH_3$ ,  
R and  $R^4$  are acyl groups

Example No.	R	$R^4$	Starting material Example No.	Process of Example No.	M.p. °C
46	COCH <sub>3</sub>	CHO	15 (16)	2, 30	142-144
47	COCF <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	28, 44	212-214
48	COCH <sub>3</sub>	COC <sub>2</sub> H <sub>5</sub>	15 (16)	28, 44	155-157
49	COC <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	28, 44	168-170
50	COCH <sub>3</sub>	CO-C(CH <sub>3</sub> ) <sub>3</sub>	15 (16)	31	201-203
51	CO-C(CH <sub>3</sub> ) <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	31	138-140
52	COCH <sub>3</sub>	CO-CH <sub>2</sub> -OCH <sub>3</sub>	15 (16)	2, 30	118-120
53	CO-CH <sub>2</sub> -OCH <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	2, 30	136-138 (d)
54	COCH <sub>3</sub>	CO-CH <sub>2</sub> -CN	15 (16)	2, 30	149-151 (d)
55	CO-CH <sub>2</sub> -CN	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	2, 30	128-130 (d)
56	CO-C <sub>6</sub> H <sub>5</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	31	154-156
57	COCH <sub>3</sub>	CO-C <sub>6</sub> H <sub>5</sub>	15 (16)	31	214-216

Table 10 (contd.)

Example No.	R	R <sup>4</sup>	Starting material Example No.	Process of Example No.	M.p. °C
58	CO-(CH <sub>2</sub> ) <sub>3</sub> -COOH	COCH <sub>3</sub>	(III), R <sup>4</sup> = COCH <sub>3</sub>	14	172-174
59	COCH <sub>3</sub>	CO-(CH <sub>2</sub> ) <sub>3</sub> -COOH	15 (16)	14	210-212 (d)
60	CHO	COC <sub>2</sub> H <sub>5</sub>	(III), R <sup>4</sup> = COC <sub>2</sub> H <sub>5</sub>	2	185-187
61	CHO	CO-C(CH <sub>3</sub> ) <sub>3</sub>	(III), R <sup>4</sup> = CO-C(CH <sub>3</sub> ) <sub>3</sub>	2	220-221 (d)
62	COCH <sub>3</sub>	COCF <sub>3</sub>	15 (16)	28	150-152 (d)
63	CHO	CO-C <sub>6</sub> H <sub>5</sub>	(III), R <sup>4</sup> = CO-C <sub>6</sub> H <sub>5</sub>	2	202-203 (d)
64	COCH <sub>3</sub>	CO-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	(III), R <sup>4</sup> = CO-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	2	135-137
65	COC <sub>2</sub> H <sub>5</sub>	CHO	18	2	140-141 (d)

(d) = decomposition

Example 66

1-(4-Glycylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepin



To a suspension of 2.89 g (5.97 mmol) of 1-(4-phthaloylglycylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (Example 79) in 50 ml of methanol 0.6 ml (11.9 mmol) of 100 % hydrazine hydrate was added and the mixture was refluxed for 2 hours. The reaction mixture was cooled, evaporated under reduced pressure, the partially crystalline residue was mixed with 40 ml of dichloromethane, filtered and the by-product was washed with 2x10 ml of dichloromethane. The solution was extracted with 3x15 ml of 5 % hydrochloric acid, the aqueous layer was made alkaline with 24 ml of aqueous 10 % sodium hydroxide, the precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 100 °C to obtain 1.67 g of raw product. After recrystallization from 73 ml of ethanol 1.50 g (71.8 %) of the aimed product were obtained, m.p.: 223-225 °C.

$C_{19}H_{18}N_4O_3 = 350.385$

#### Examples 67 to 78

Other compounds of the general formula (I), wherein  $R^2 = CH_3$ ,  $R^3 = H$ , and some of their acid addition salts, prepared by the process of Example 66, are presented in Table 11. The salts were prepared by known methods.

Table 11

Example No.	R	R <sup>1</sup>	R <sup>4</sup>	Example No. of starting material	M.p. °C (salt)
67	-	-	CO-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	80	198-200 (d)
68	-	-	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	81	155-157 (d)
69	-	-	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	68	217-219 (d) (H-Fu)
70	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	H	82	150-155
71	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	H	70	190-193 (d) (H-Fu)
72	DL -CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	H	H	84	193-195
73	COCH <sub>3</sub>	H	CO-CH <sub>2</sub> -NH <sub>2</sub>	88	(H-Fu 210-213 (d) ) 210-211 (d) (HCl) [base 230-232 (d) ]
74	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	COCH <sub>3</sub>	89	210-212 (d)
75	CO-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	H	COCH <sub>3</sub>	90	154-156 (d) (Fu)
76	(H-Fu), COCH <sub>3</sub>	H	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	91	222-223 (d) (H-Fu)
77	DL -CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	H	COCH <sub>3</sub>	92	218-220 (d)
78	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	CO-CH <sub>2</sub> -NH <sub>2</sub>	93	202-204 (d)

Notes: H-Fu = hydrogen fumarate (H-fumarate), Fu = fumarate

The products of Examples 70 to 72 were prepared from the corresponding starting substances in two steps, by following first Example 66 and then Example 16.

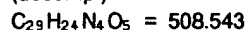
Example 79

1-[4-(N-Phthaloylglycylamino)ph nyl]-4-m thyl-7,8-methyl nedioxy-5H-2,3-b nzodiaz pin

To a solution of 2.0 g (6.88 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane 1.84 g (8.94 mmol) of dicyclohexylcarbodiimide and 1.84 g (8.94 mmol) of powdered phthalimidoacetic acid were added and the reaction mixture was stirred at 25 °C for 8 hours, then left to stand at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x3 ml of dichloromethane and dried at 60-80 °C to result in 5 g of a product consisting of a mixture of the target product and N,N'-dicyclohexylurea, a by-product. This mixture was purified by refluxing with 210 ml of ethanol for 30 minutes, filtering the hot mixture and washing with 2x10 ml of hot ethanol, thereafter drying at 100 °C to obtain 2.42 g (73.3 %) of the aimed product, m.p.: 266-268 °C (decomp.).  
 $C_{27}H_{20}N_4O_5 = 480.489$

**Example 80****1-[4-(N-Phthaloyl-γ-aminobutyrylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

By following the process described in Example 79 but using γ-phthalimidobutyric acid, 3.8 g of a mixture were obtained, which was combined with the dichloromethane mother liquor extracted previously with 2x40 ml of a 10 % aqueous sodium carbonate solution. After evaporating under reduced pressure the residue was submitted to column chromatography [adsorbent: Kieselgel 60 (0.063-2 mm), eluent: ethyl acetate:methanol 4:1]. The evaporation residue was triturated with 10 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried to give 3.12 g (90 %) of the aimed product, m.p.: 233-235 °C (decomp.).

**Example 81****1-[4-(M-Phthaloyl-DL-alanyl-amino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

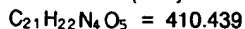
The process described in Example 79 was followed, except that N-phthaloyl-DL-alanine (DL-2-phthalimido-propionic acid) was used. After filtering the slight precipitate formed the filtrate was evaporated, the residue was mixed with 15 ml of dichloromethane, carefully filtered and the clear solution obtained was repeatedly evaporated. The purification of the residue was achieved by refluxing it with 60 ml of ethyl acetate. Crystal formation was already started in the hot solution. The crystals were filtered at 0-5 °C, the nearly white crystal powder was washed with 3x3 ml of ethyl acetate and dried at 100 °C to give 2.75 g (80.95 %) of the aimed product, m.p.: 243-245 °C (decomp.).

**Example 82****1-(4-Nitrophenyl)-3-glycyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

The process described in Example 66 was followed by using the compound prepared according to Example 85 as starting material, but the dichloromethane solution was extracted only with 3x20 ml of distilled water and the organic layer was evaporated under reduced pressure. The crystalline residue was purified by suspending it in 7 ml of ethanol to give the pure aimed product in a yield of 86.1 %, m.p.: 201-203 °C (decomp.).

**Example 83****1-(4-Nitrophenyl)-3-(γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

By following the process described in Example 82 and using the compound prepared according to Example 86 as starting material, a product containing crystal solvent was obtained in a yield of 89.4 %, m.p. 110-112 °C (recrystallized from 50 % ethanol).

**Example 84**

**1-(4-Nitrophenyl)-3-(DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

By following the process described in Example 82 and using the compound prepared according to Example 87 the aimed compound was obtained, m.p. 220-221 °C (decomp.).

$C_{20}H_{20}N_4O_5 = 396.412$

**Examples 85 to 87**

The new intermediates employed in Examples 82 to 84 as starting materials were prepared from the compound prepared according to Example 26 by the process of Example 81.

**Example 85**

**1-(4-Nitrophenyl)-3-(N-phthaloylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

Yield: 93.3 %, m.p.: 173-174 °C (decomp.).

$C_{27}H_{20}N_4O_7 = 512.489$

**Example 86**

**1-(4-Nitrophenyl)-3-(N-phthaloyl-γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 218-220 °C

$C_{29}H_{24}N_4O_7 = 540.543$

**Example 87**

**1-(4-Nitrophenyl)-3-(N-phthaloyl-DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 210-212 °C

$C_{28}H_{22}N_4O_7 = 526.516$

**Example 88 to 94**

The intermediates of the general formula (I), wherein R and/or R<sub>4</sub> represent(s) C<sub>1-6</sub> acyl group(s) substituted by a phthalimido group, are required for the preparation of compounds obtained by using the processes of Examples 73 to 78 and summarized in Table 12. They were prepared from the compound of Example 15 (16) or from a compound of the general formula (III), wherein R<sub>4</sub> is hydrogen (see U.S. patent specification No. 4,835,152) or from 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine described hereinabove (before Table 10) by following the process of Example 81.

As a matter of course, in Example 93 a twofold amount of phthaloylglycine and dicyclohexylcarbodiimide have to be used. Thus, Table 12 lists new compounds of the general formula (I), wherein R and R<sup>4</sup> are acyl groups, R<sup>1</sup> = R<sup>3</sup> = H and R<sup>2</sup> = CH<sub>3</sub>.

Table 12

Example No.	R	R <sup>4</sup>	M.p. °C
88	COCH <sub>3</sub>	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	314-316 (d)
89	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	204-206 (d)
90	CO-(CH <sub>2</sub> ) <sub>3</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	150-152
91	COCH <sub>3</sub>	DL -CO-CH(CH <sub>3</sub> )-N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	264-266 (d)
92	DL -CO-CH(CH <sub>3</sub> )-N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	245-248
93	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	230-232 (d)
94	COCH <sub>3</sub>	CO-(CH <sub>2</sub> ) <sub>3</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	173-175

(CO)<sub>2</sub>C<sub>6</sub>H<sub>4</sub> = phthaloyl; N(CO)<sub>2</sub>C<sub>6</sub>H<sub>4</sub> = phthalimido; (d) = decomposition

## Exempl 95

1-(4-Aminoph nyl)-3-(γ-aminobutyryl)-4-m thyl-7,8-methylen dioxy-3,4-dihydr -5H-2,3-benzodiazepine hydrogen fumarate

It was prepared from the compound of Example 83 by following Example 16, m.p.: 150-152 °C (decomp.)

$[C_{29}H_{25}N_4O_3] \cdot C_4H_3O_4 = 496.531$

**Example 96**

5 **1-(4-Aminophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrochloride**

It was obtained from the compound of Example 37, according to Example 16, m.p.: 224-226 °C (decomp.).

10  $[C_{22}H_{24}N_3O_5]Cl = 445.915$

**Example 97**

**1-(4-Trifluoroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

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It was prepared by following Example 2, m.p.: 258-260 °C (decomp.).

$C_{19}H_{14}F_3N_3O_3 = 389.339$

**Example 98**

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**1-(4-Aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-nitrophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to Example 16, m.p. 199-201 °C.

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$C_{19}H_{20}N_4O_3 = 352.401$

Hydrochloride m.p. 219-221 °C (decomp.).

$[C_{19}H_{21}N_4O_3]Cl = 388.866$

The starting nitro compound was prepared as follows:

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1.1 ml (18.4 mmol) of methyl isocyanate were added to 3.0 g (9.22 mmol) of 1-(4-nitrophenyl)-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 26) dissolved in 60 ml of dichloromethane and stirred for 24 hours, then evaporated under reduced pressure. The crystalline residue was triturated with 30 ml of hot ethanol at 80 to 100 °C to obtain 3.35 g (95 %) of the lemon-yellow aimed product, m.p.: 238-240 °C (decomp.).

35

$C_{19}H_{18}N_4O_5 = 382.385$

**Example 99**

40 **1-(4-Aminophenyl)-3-(1-pyrrolidinoacetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was obtained from 1-(4-nitrophenyl)-3-(1-pyrrolidino-acetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by following Example 16, m.p.: 212-214 °C.

$C_{23}H_{26}N_4O_3 = 406.493$

45

The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 116) according to Example 102, m.p.: 189-190 °C (decomp.).

$C_{23}H_{24}N_4O_5 = 436.477$

50

**Example 100**

**1-(4-Aminophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine fumarate**

55

It was prepared from 1-(4-nitrophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to Example 16, m.p.: 202-204 °C (decomp.).

$[C_{21}H_{25}N_4O_3]C_4H_3O_4 = 496.531$

The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-

3,4-dihydro-5H-2,3-benzodiazepine according to the process described in Example 103, m.p.: 158-160 °C.  
 $C_{21}H_{22}N_4O_5 = 410.439$

**Example 101**

**1-(4-Chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

It was prepared according to Example 2, except that chloroacetic acid was used, m.p.: 209-214 °C (carbonization).

$C_{19}H_{16}ClN_3O_3 = 369.818$

**Example 102**

**1-[4-(1-Pyrrolidinoacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

0.71 ml (8.53 mmol) of pyrrolidine was added to a suspension of 1.5 g (4.06 mmol) of 1-(4-chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol and the reaction mixture was refluxed for 4 hours, then evaporated under reduced pressure. The residue was treated with water to give a rough product (1.49 g), m.p.: 186-188 °C. After recrystallization from 12 ml of ethanol 1.22 g (74.4 %) of the aimed product were obtained, m.p.: 210-212 °C.

$C_{23}H_{24}N_4O_3 = 404.477$

**Example 103**

**1-[4-(N,N-dimethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

After adding 0.66 g (8.12 mmol) of dimethylamine hydrochloride and 1.86 ml (13.4 mmol) of triethylamine to a suspension of 1.5 g (4.06 mmol) of 1-(4-chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol, the reaction mixture was refluxed for 8 hours, then evaporated. The residue was dissolved in 30 ml of dichloromethane, washed with 20 ml of 4 % NaOH solution, then 2x20 ml of distilled water, dried and evaporated under reduced pressure. After treating with water, the crystalline residue was filtered to give 1.27 g of raw product, m.p. 211-213 °C. After recrystallization from 10 ml of ethanol 1.1 g (71.4 %) of aimed product were obtained, m.p.: 213-215 °C.

$C_{21}H_{22}N_4O_6 = 378.439$

**Example 104**

**1-(4-Methylcarbamoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

0.8 ml (13.4 mmol) of methyl isocyanate was added to a solution containing 1.0 g (3.41 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 8 ml of dimethylformamide (DMF), then the reaction mixture was stirred at 25 °C for 24 hours. After diluting with 80 ml of water, filtering at 5 °C and drying at 60 to 100 °C, 1.06 g of raw product, m.p.: 204-207 °C (sintering from 160 °C) were obtained which, when recrystallized from 5 ml of ethanol, gave 0.85 g (71.4 %) of the aimed product, m.p.: 223-224 °C (decomp.).

$C_{19}H_{18}N_4O_3 = 350.385$

**Example 105**

**1-(4-Acetylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 42. The raw product was recrystallized from ethyl acetate to give 71.4 % of the aimed product, m.p.: 150-152 °C.

$C_{21}H_{22}N_4O_4 = 394.439$

**Exempl 106**

**1-(4-Chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2, m.p.: 139-140 °C.  $C_{21}H_{20}ClN_3O_4 = 413.972$

**Example 107**

**1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from the product of the preceding Example by using the process described in Example 103, m.p.: 206-208 °C.  
 $C_{23}H_{26}N_4O_4 = 422.493$

**Example 108**

**1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and diethylamine by using the process described in Example 102, m.p.: 175-176 °C.  
 $C_{25}H_{30}N_4O_4 = 450.547$

**Example 109**

**1-[4-(1-Pyrrolidinoacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate**

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2 and isolated in the form of hydrogen fumarate, m.p.: 181-183 °C (decomp.).  
 $[C_{25}H_{29}N_4O_4] \cdot C_4H_3O_4 = 564.607$

**Example 110**

**1-(4-Acetylaminophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from the compound of general formula (III), wherein  $R^4 = COCH_3$ , by using the process of Example 2 and chloroacetic acid instead of formic acid, m.p. 138-140 °C.  
 $C_{21}H_{20}ClN_3O_4 = 413.972$

**Example 111**

**1-[4-(N,N-diethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

It was prepared from 1-(4-chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine by using the process of Example 102, except that diethylamine was used instead of pyrrolidine, m.p.: 157-158 °C.  
 $C_{23}H_{26}N_4O_3 = 406.493$

**Example 112**

**1-(4-Acetylaminophenyl)-3-cyclopropanecarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**



It was prepared from 1-(4-aminophenyl)-3-cyclopropane-carbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 42, m.p.: 242-243 °C.

$C_{23}H_{23}N_3O_4 = 405.461$

#### 5 Example 113

**N<sup>1</sup>-[4-(3-Methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-methylurea**

10 After adding 0.5 ml (8.5 mmol) of methyl isocyanate to 0.6 g (1.7 mmol) of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) dissolved in 45 ml of anhydrous dichloromethane, the reaction mixture was stirred at 25 °C for 6 days. Then the crystalline precipitate was filtered, washed with 3x2 ml of dichloromethane and dried at 60 to 80 °C to obtain 0.55 g (79.7 %) of the pure aimed product, m.p.: 181--183 °C.

15  $C_{21}H_{23}N_5O_4 = 409.455$

#### Example 114

20 **1-(4-Aminophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-nitrophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine, m.p.: 173-175 °C.

$C_{22}H_{26}N_4O_3 = 394.482$

25 The starting substance was prepared as described for the starting substance of Example 98, except that n-butyl isocyanate was used instead of methyl isocyanate and the reaction mixture was stirred for 5 days at 25 °C, m.p. 176-178 °C.

$C_{22}H_{24}N_4O_3 = 424.466$

#### 30 Example 115

**1-(4-Glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

35 It was prepared from 1-[4-(N-phthaloylglycylamino)-phenyl]-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 66 as modified in Example 82, m.p.: 163-165 °C.

$C_{21}H_{23}N_5O_4 = 409.455$

40 The starting substance was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) according to Example 79, m.p. 270-271 °C (decomp.).

$C_{29}H_{25}N_5O_6 = 539.559$

#### Example 116

45 **1-(4-Aminophenyl)-3-(N-methylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

50 1.03 g (15.3 mmol) of methylamine hydrochloride and 2.64 ml (18.3 mmol) of triethylamine were added to a suspension containing 1.23 g (3.06 mmol) of 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 140 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was dissolved in 30 ml of chloroform, washed with 20 ml of 4% NaOH solution, then 2x20 ml of water, dried and evaporated under reduced pressure. The residue was reduced according to the process of Example 16 and the product obtained was purified by column chromatography (adsorbent: Kieselgel 60, eluent: methanol - benzene 4:1). The crude product obtained was triturated with 5 ml of ethyl acetate at 25 °C to obtain 0.60 g (53.6 %) of the aimed product, m.p. 198-200 °C (weak decomp.).

$C_{20}H_{22}N_4O_3 = 366.428$

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The starting compound was obtained from 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 26) and chloroacetic acid by using the process of Example 33, m.p. 189-191 °C (decomp.).

$C_{19}H_{16}ClN_3O_5 = 401.818$

## Example 117

### 1-[4-(N-methylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.31 g (19.5 mmol) of methylamine hydrochloride and 3.24 ml (23.3 mmol) of triethylamine were added to a suspension containing 1.61 g (3.89 mmol) of 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 106) in 100 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was purified by column chromatography (adsorbent: Kieselgel 60, eluent: chloroform - methanol 9:1). The crude product was triturated with 3 ml of 50 % ethanol at 25 °C to give 0.61 g (38.6 %) of the aimed product, m.p.: 220-222 °C (weak decomp.).

$C_{22}H_{24}N_4O_4 = 408.466$

## Example 118

### Preparation of pharmaceutical compositions

Tablets or divided tablets containing 25 mg of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Examples 15 or 16) or 25 mg of 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 42) or 25 mg of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 98) each as active ingredient were prepared by usual methods.

#### a) Composition of one tablet:

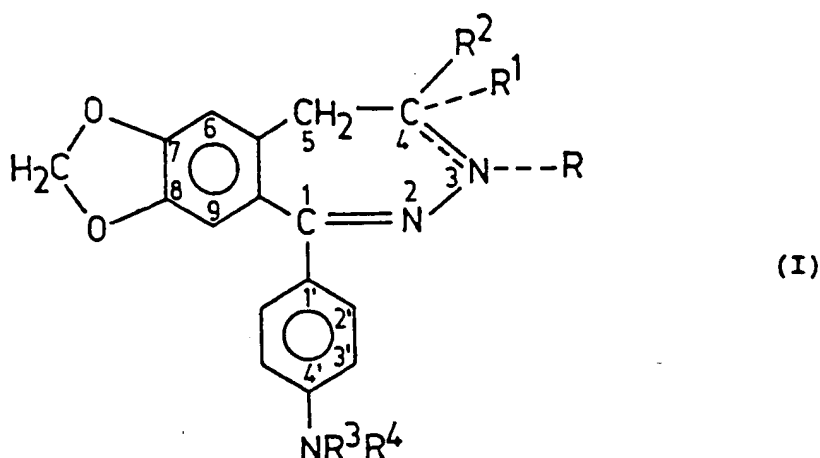
Active ingredient	25 mg
Potato starch	43 mg
Lactose	160 mg
Polyvinylpyrrolidone	6 mg
Magnesium stearate	1 mg
Talc	30 mg

#### b) An other preferred composition of one tablet:

Active ingredient	25 mg
Lactose	130 mg
Maize starch	25 mg
Microcrystalline cellulose	10 mg
Gelatine	4 mg
Talc	2 mg
Stearin	1 mg
Magnesium stearate	1 mg

## Claims

1. N-Acyl-2,3-benzodiazepine derivatives of the general formula (I)



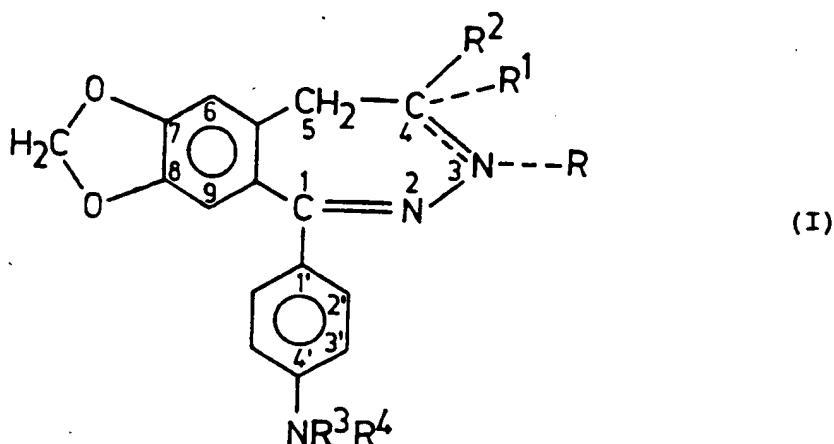
wherein

- R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or
- R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;
- R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;
- R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and
- the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen, and their stereoisomers as well as acid-addition salts (where possible) of these compounds.

2. A compound selected from the group consisting of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4 -dihydro-5H-2,3-benzodiazepine,
- 1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylene -dioxo-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylene -dioxo-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-propionylaminophenyl)-3-formyl-4-methyl-7,8-methylene -dioxo-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine hydrochloride,
- N<sup>1</sup>-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H -2,3-benzodiazepine-1-yl)-phenyl]-N<sup>3</sup>-methylurea,
- 1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,

1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-[4-(1-pyrrolidinoacetylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine  
 and hydrogen fumarate thereof and  
 1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

3. A pharmaceutical composition, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.
4. A process for the preparation of the novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I),



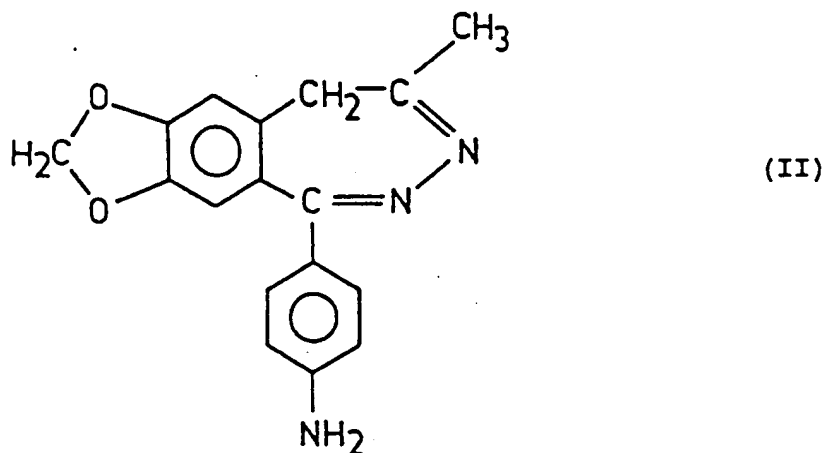
wherein

- R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or
- R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;
- R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;
- R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen,

and their stereoisomers as well as acid addition salts, which comprises

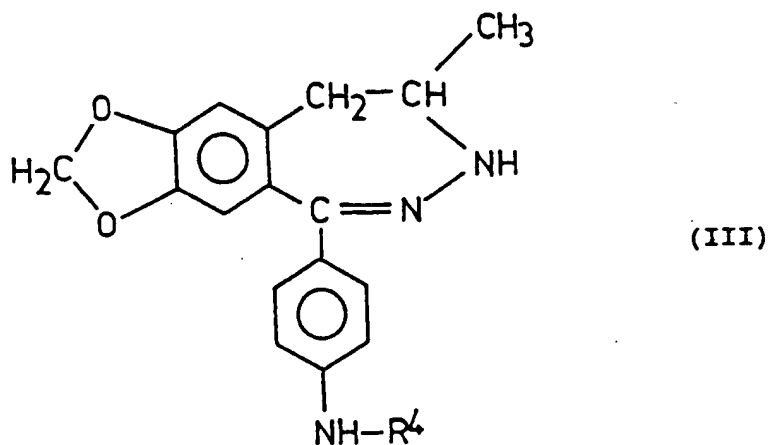
- a) acylating a compound of formula (II)



20 with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine,

25 to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

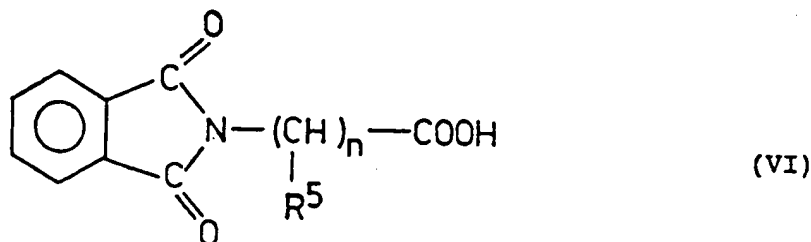
30 b) acylating a compound of the general formula (III),



50 wherein R<sup>4</sup> is as defined above, with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined above, R means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

55

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



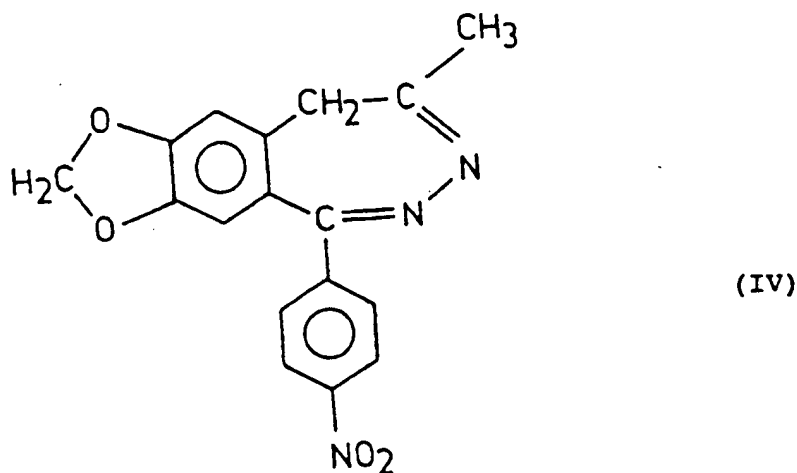
15 wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> stands for a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group, both R and R<sup>1</sup> are absent, and a double bond is present between the N(3) and C(4) atoms; or

20 d) acylating a compound of the general formula (III), wherein R<sup>4</sup> is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> is as defined above except hydrogen, R stands for a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

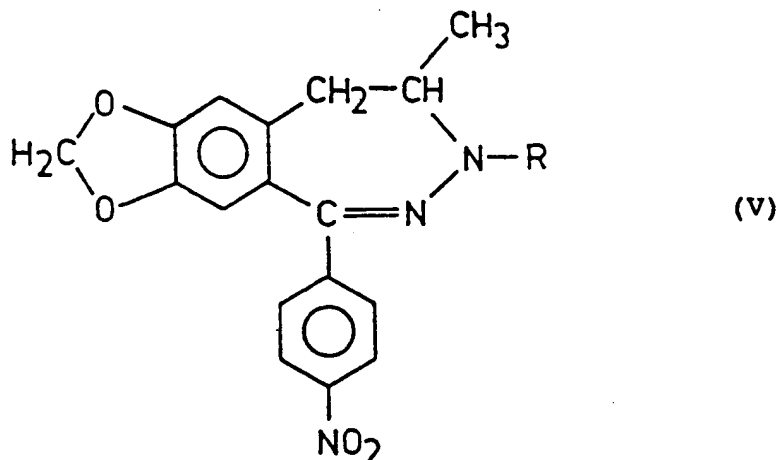
25 e) reacting a compound of the formula (II) with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group, R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms; or

30 f) reacting a compound of the general formula (III), wherein R<sup>4</sup> is defined as above, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> means hydrogen, R<sup>4</sup> is as defined above except hydrogen, R stands for a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

35 g) selectively reducing a nitro compound of the formula (IV)



to a novel compound of the general formula (V)



20 wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R<sup>4</sup> stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> represent hydrogen, R<sup>2</sup>, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

25 h) acylating a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R and R<sup>4</sup> represent a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

30 i) reacting a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen; R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

35 j) acylating a new compound of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R represents a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen, R<sup>4</sup> represents a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

40 and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

- 55 5. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.

6. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the presence of an acid-binding agent at a temperature between 0 °C and 150 °C.
7. A process as claimed in claim 6, which comprises carrying out the reaction in chloroform or dichloromethane.
8. A process as claimed in claim 4, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.
9. A process as claimed in claim 4, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C<sub>1-4</sub> aliphatic alcohol solution.
10. A process as claimed in claim 4, process g) or claim 6, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.
11. A process for the preparation of the pharmaceutical composition according to claim 3, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.
12. The use of the compounds prepared according to claims 1 to 8 for preparing medicaments, particularly such blocking one or more excitatory amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or such for treating epilepsy in mammals, or such for treating spasms of the skeletal musculature in mammals by muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals.
13. N-Acyl-2,3-benzodiazepine derivatives of the general formula V, wherein  
R means hydrogen or a C<sub>1-6</sub> aliphatic acyl group; optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group.

Claims for the following Contracting States : GR, ES

1. A process for the preparation of N-acyl-2,3-benzodiazepine derivatives of the general formula (I),

R<sup>2</sup>



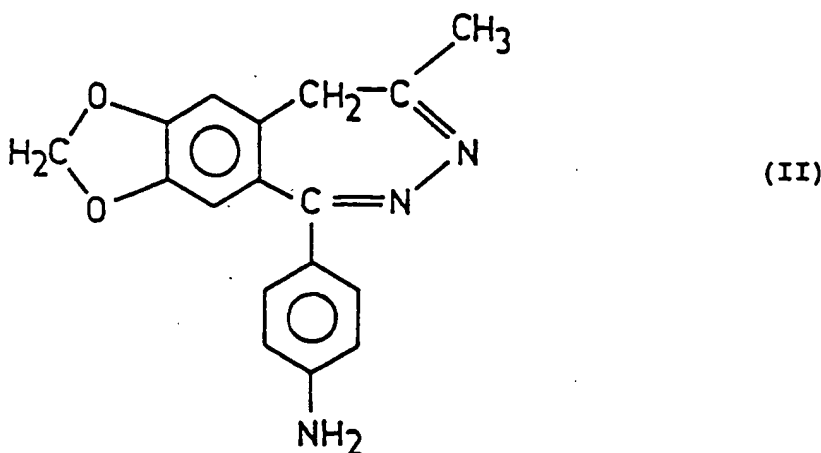
wherein

- R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or
- R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;
- R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;
- R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen,

and their stereoisomers as well as acid addition salts, which comprises

a) acylating a compound of formula (II)

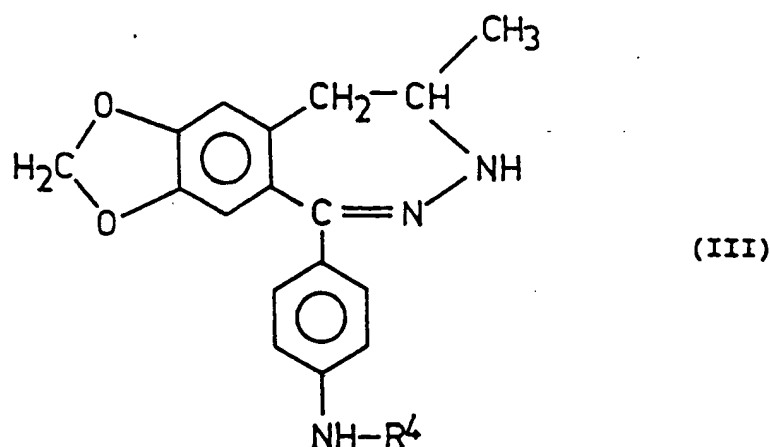


with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine,

di(C<sub>1-4</sub> alkyl)amine or pyrrolidine,

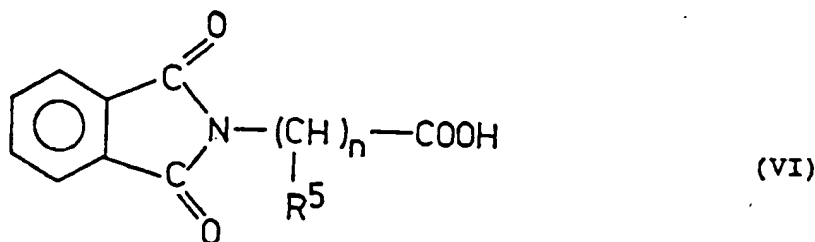
to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

b) acylating a compound of the general formula (III),



wherein  $R^4$  is as defined above, with a  $C_{1-6}$  aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein  $R^4$  means a  $C_{1-6}$  aliphatic acyl group substituted by a halogen, with a  $C_{1-4}$  alkylamine, di( $C_{1-4}$  alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and the dotted lines are as defined above,  $R$  means a  $C_{1-6}$  aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl,  $C_{1-4}$  alkylamino, di( $C_{1-4}$  alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



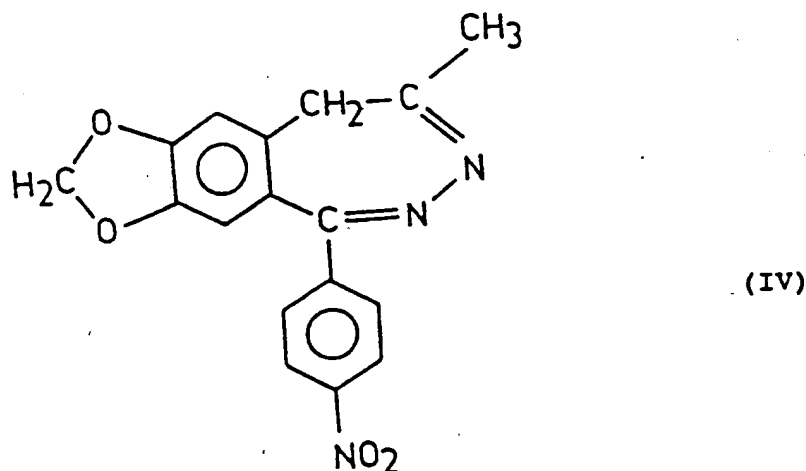
wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group, both  $R$  and  $R^1$  are absent, and a double bond is present between the N(3) and C(4) atoms; or

d) acylating a compound of the general formula (III), wherein  $R^4$  is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen,  $R$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

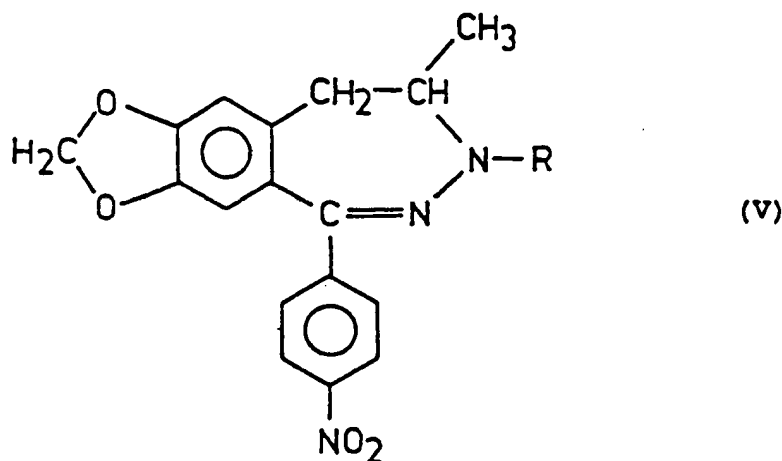
e) reacting a compound of the formula (II) with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  represents a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group,  $R$  and  $R^1$  are absent and a double bond is present between the N(3) and C(4) atoms; or

f) reacting a compound of the general formula (III), wherein  $R^4$  is defined as above, with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen,  $R$  stands for a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

g) selectively reducing a nitro compound of the formula (IV)



to a novel compound of the general formula (V)



wherein  $R$  means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein  $R$  is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein  $R^4$  stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^3$  and  $R^4$  represent hydrogen,  $R^2$ ,  $R$  and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein  $R$ ,  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  and  $R^4$  mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a  $C_{1-6}$  aliphatic carboxylic acid, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative

thereof, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R and R<sup>4</sup> represent a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen; R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbonyl or phenylcarbonyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of  $\alpha$ -amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of  $\beta$ -amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R represents a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen, R<sup>4</sup> represents a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

2. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.

3. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the presence of an acid-binding agent at a temperature between 0 °C and 150 °C.

4. A process as claimed in claim 3, which comprises carrying out the reaction in chloroform or dichloromethane.

5. A process as claimed in claim 1, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.

6. A process as claimed in claim 1, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C<sub>1-4</sub> aliphatic alcohol solution.

7. A process as claimed in claim 1, process g) or claim 3, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.

8. A process according to anyone of claims 1 to 7, characterized in that a compound selected from the group consisting of

1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4	-dihydro-5H-2,3-benzodiazepine,
1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy	-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy	-3,4-dihydro-5H-2,3-benzodiazepine,
1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8	-methylenedioxy-3,4-dihydro-5H-2,3-
benzodiazepine,	
1-(4-propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylene	-dioxy-3,4-dihydro-5H-2,3-
benzodiazepine,	
1-(4-acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylene	-dioxy-3,4-dihydro-5H-2,3-
benzodiazepine,	

1-(4-propionylaminophenyl)-3-formyl-4-methyl-7,8-methylene -dioxy-3,4-dihydro-5H-2,3-  
benzodiazepine,  
1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-  
benzodiazepine,  
5 1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy -3,4-dihydro-5H-2,3-benzodiazepine  
hydrochloride,  
N'-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H -2,3-benzodiazepine-1-yl)-phenyl]-N<sup>3</sup>-  
methylurea,  
10 1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-  
benzodiazepine,  
1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-  
benzodiazepine,  
1-[4-(1-pyrrolidinocetylaminophenyl)-3-acetyl-4-methyl -7,8-methylenedioxy-3,4-dihydro-5H-2,3-  
benzodiazepine  
15 and hydrogen fumarate thereof and  
1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8 -methylenedioxy-3,4-dihydro-5H-2,3-  
benzodiazepine is prepared.

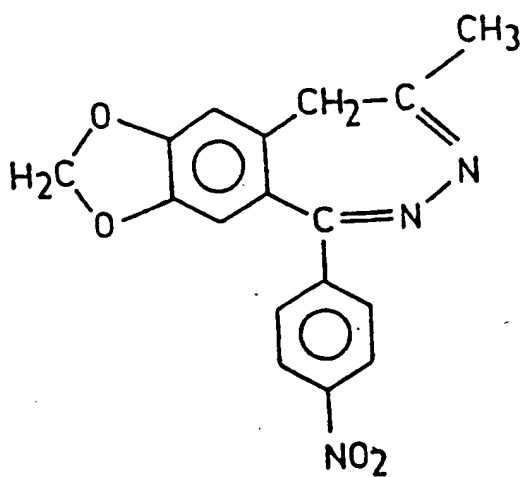
9. A process for the preparation of a pharmaceutical composition which comprises as  
20 active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>,  
R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid  
addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical  
industry, characterized by admixing as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of  
25 the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a  
pharmaceutically acceptable acid addition salt thereof, prepared by using any of process variants a) to  
j) as claimed in claim 1, with carriers and/or additives commonly used in the pharmaceutical industry  
and transforming them to a pharmaceutical composition.

10. A process according to claim 9, characterized in that compositions for blocking one or more excitatory  
30 amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or for  
treating epilepsy in mammals, or for treating spasms of the skeletal musculature in mammals by  
muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals are prepared.

11. A process for preparing N-acyl-2,3-benzodiazepine derivatives of the general formula V,  
35 wherein

R means hydrogen or a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano,  
carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl  
group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub>  
alkylcarbamoyl or phenylcarbamoyl group,

40 characterized by selectively reducing a nitro compound of the formula selectively reducing a nitro  
compound of the formula (IV)



(IV).



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 91 12 1882

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
Y	GB-A-2 194 236 (BIOGAL GYOGYSZERGYAR)  * page 1, line 40 - line 54; claims 1-5,8-10 * D & US-A-4 835 152	1,3,4, 11,12	C07D491/04 A61K31/55 //(C07D491/04, 317:00,243:00)
Y	GB-A-2 162 184 (EGIS GYOGYSZERGYAR)  * page 2, line 41 - line 48; claims 1-3,9,10; examples 5,8 * D & US-A-4 614 740	1,3,4, 11,12	
Y	CHEMICAL ABSTRACTS, vol. 111, no. 21, 20 November 1989, Columbus, Ohio, US; abstract no. 187314F, I. TARNAMA ET AL.: 'Electrophysiological studies with ...' page 58 ; & Eur. J. Pharmacol. 1989, 167(2), 193-9	1,12	
Y	DE-A-2 353 187 (KALI-CHEMIE AG)  * claim 1; page 5, last paragraph to page 6, line 18; page 11, lines 15-19; pages 15-17 *	1,3,4, 11,12	TECHNICAL FIELDS SEARCHED (Int. CL.5)
A,D	FR-A-2 566 774 (EGIS GYOGYSZERGYAR) * claim 5; page 20, table V *	13	C07D
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 20 MARCH 1992	Examiner CHRISTIAN HASS
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

(19)



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243:00)

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(54) **N-Acyl-2,3-benzodiazepine derivatives, pharmaceutical compositions containing them and process for preparing same**

N-Acyl-2,3-benzodiazepin-Derivate, diese enthaltende pharmazeutische Zusammensetzungen und Verfahren zu ihrer Herstellung

Dérivés de N-acyl-2,3-benzodiazépine, compositions pharmaceutiques les contenant et procédé pour leur préparation

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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**EP 0 492 485 B1**



## Description

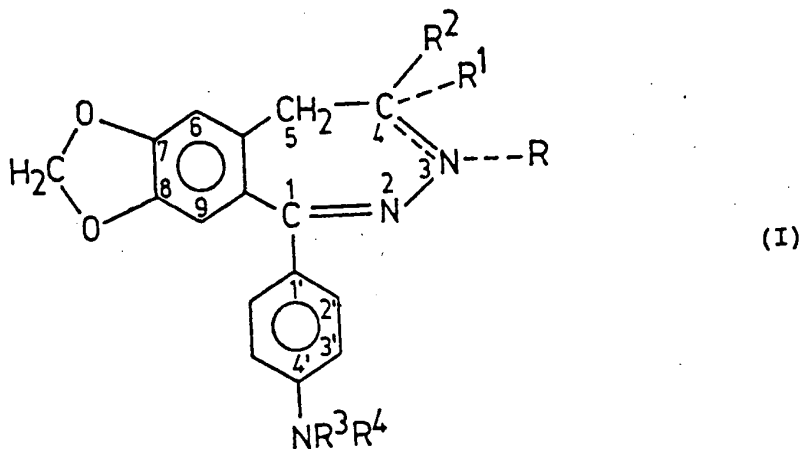
This invention relates to novel N-acyl-2,3-benzodiazepine derivatives.

From GB 2,194,236 A there have been known 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and acid-addition salts thereof. Activity on the central nervous system and the use in the therapy of CNS stimulant and dopamine agonists have been indicated for these. In GB 2,162,184 A inter alia 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives and acid-addition salts thereof have been described. For these compounds central nervous effects, e.g. antiaggressive, anxiolytic, narcosis potentiating and hypnotic effects have been indicated. FR-A-2 566 774 1-phenyl-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine derivatives have been described. For these compounds activity on the central nervous system, e.g. antiaggressive and soporific effects have been indicated. In none of these publications muscle-relaxant or anticonvulsive effects have been indicated for the compounds described there.

In Chemical Abstracts 1989, 111: 187314f, for the compound 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine, muscle-relaxant and anticonvulsive properties have been indicated.

From DE-A-2 353 187 there have been known 2-acyl imido, 5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine derivatives which may be substituted by a methylenedioxy group. It has been indicated that they can be used as tranquilizers having small musculotropic properties.

This invention relates to novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I)



wherein

R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms; means hydrogen; or R¹ is absent when a double bond exists between the N(3) and C(4) atoms; means a C<sub>1-3</sub> alkyl group; or R¹ and R² together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms; means hydrogen or a C<sub>1-4</sub> aliphatic acyl group; represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R³ and R⁴ stand for hydrogen, and their stereoisomers as well as acid addition salts (where possible) and pharmaceutical compositions containing these compounds.

As number of carbon atoms in the respective groups 1 to 4 (so far as not anyhow the upper limit is 4), particularly 1 or 2, is preferred. From the halogen atoms fluorine and chlorine are preferred. In case of fluorine atoms preferably 3

of them are present as substituents.

The compounds of general formula (I) according to the invention have an asymmetric molecular structure. The general formula (I) relates to all possible individual stereoisomers and their mixtures.

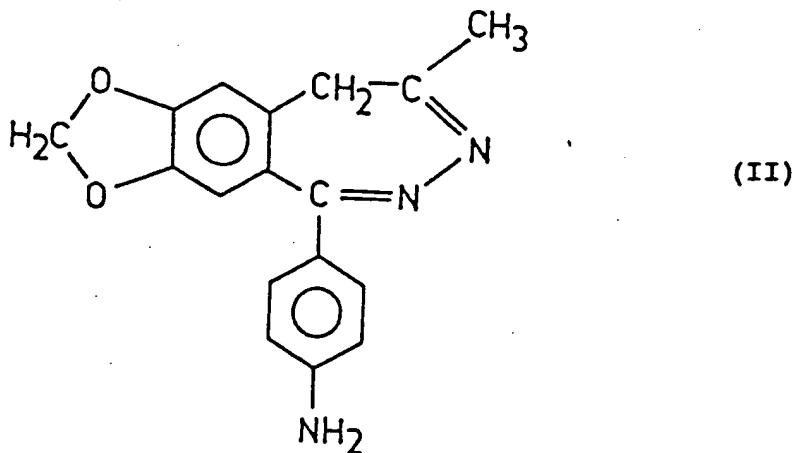
According to another aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I) and the acid-addition salts thereof.

The aim of the present invention is to develop new compounds of the general formula (I) which possess valuable central nervous system (CNS), particularly muscle-relaxant and/or anticonvulsive, activity. A single compound showing such effect is only known among 2,3-benzodiazepines, namely 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (United States patent specification No. 4,614,740) also prepared by the authors of the present invention. In the course of detailed pharmacological screening it was revealed, however, that the above compound was positive in the Ames-test, i.e. it proved to be mutagenic. Thus, it is the specific aim of the present invention to find out novel 2,3-benzodiazepine derivatives which retain their valuable muscle-relaxant and anticonvulsive activity but are negative in the Ames test.

The new compounds of general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined above, and their pharmaceutically acceptable acid-addition salts completely satisfy this requirement.

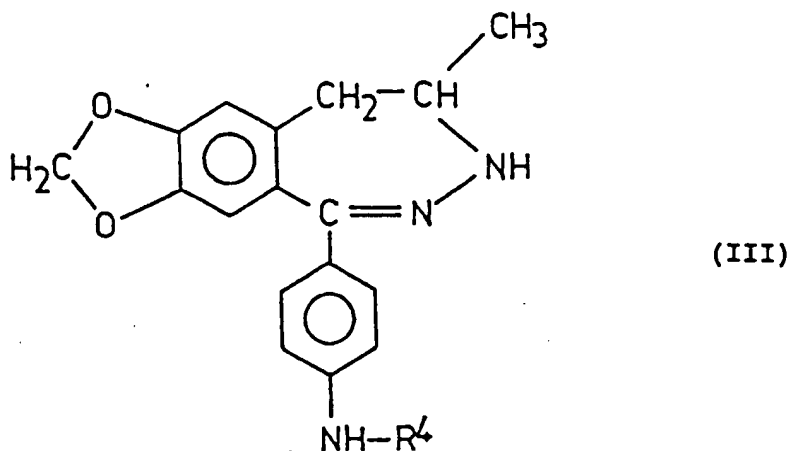
According to the invention, the compounds of general formula (I) are prepared by

a) acylating a compound of formula (II)



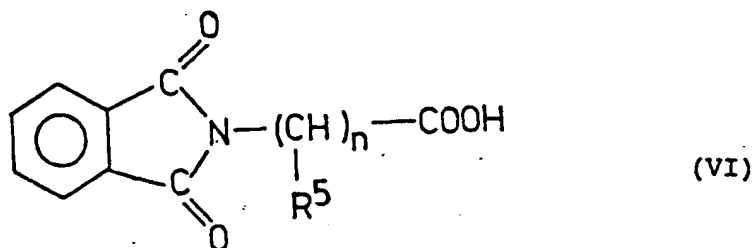
with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

b) acylating a compound of the general formula (III),



wherein  $R^4$  is as defined above, with a  $C_{1-6}$  aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein  $R^4$  means a  $C_{1-6}$  aliphatic acyl group substituted by a halogen, with a  $C_{1-4}$  alkylamine, di( $C_{1-4}$  alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and the dotted lines are as defined above,  $R$  means a  $C_{1-6}$  aliphatic acyl group optionally substituted by a methoxy, cyano, carboxy, phenyl,  $C_{1-4}$  alkylamino, di( $C_{1-4}$  alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),

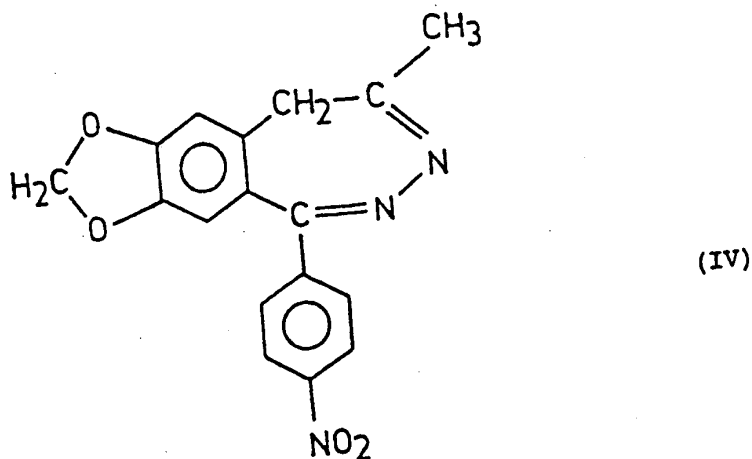


wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group, both  $R$  and  $R^1$  are absent, and a double bond is present between the N(3) and C(4) atoms; or

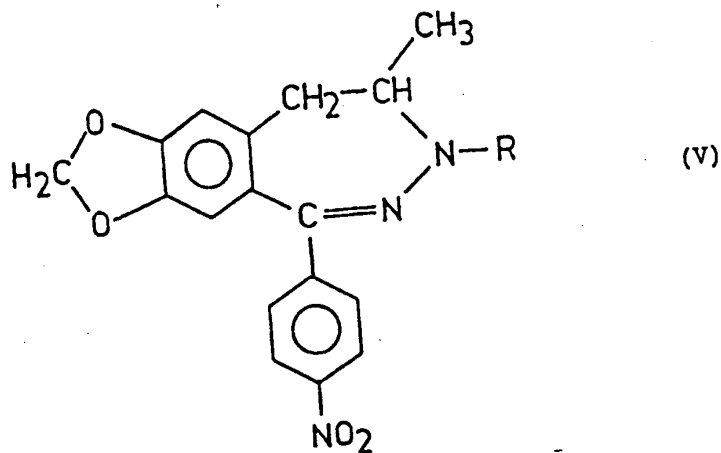
d) acylating a compound of the general formula (III), wherein  $R^4$  is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen,  $R$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

e) reacting a compound of the formula (II) with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  represents a  $C_{1-5}$  alkylcarbonyl or phenylcarbonyl group,  $R$  and  $R^1$  are absent and a double bond is present between the N(3) and C(4) atoms; or

f) reacting a compound of the general formula (III), wherein  $R^4$  is defined as above, with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as



to a novel compound of the general formula (V)



wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R<sup>4</sup> stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> represent hydrogen, R<sup>2</sup>, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R and R<sup>4</sup> represent a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above,

$R^3$  and  $R^4$  mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above, R stands for a  $C_{1-6}$  aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group;  $R^3$  stands for hydrogen;  $R^4$  represents a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  and  $R^4$  mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and n is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and n is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above, R represents a  $C_{1-6}$  aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group;  $R^3$  stands for hydrogen,  $R^4$  represents a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

According to a preferred embodiment of the process of the present invention the acylation of the compounds of the general formulae (I), (II), (III) and (V) can be carried out preferably with a suitable carboxylic acid, in the presence of dicyclohexyl-carbodiimide in a suitable solvent, preferably in dichloromethane, in a temperature range of 10 to 30 °C during 1 to 25 hours.

According to an other preferred embodiment of the present invention the compounds of the general formulae (I), (II), (III) and (V) can be acylated in a temperature range of zero to 150 °C by a suitable reactive acyl derivative, i.e. carboxylic acid anhydride, mixed anhydride or acyl chloride, in the absence or presence of a solvent usually applied in acylations of such types such as chloroform or dichloromethane, in the absence or presence of an acid-binding agent, such as triethylamine. If the additive acylation is performed with isocyanates, the reaction is advantageously carried out in dimethylformamide, benzene or dichloromethane in a temperature range of 15 to 100 °C during 0.5 to 100 hours.

The selective reduction of the compound of general formula (IV) to the compound of general formula (V), wherein R denotes a hydrogen atom, can be performed by an inorganic or inorganic-organic complex metal hydride, preferably sodium borohydride, in a solvent or solvent mixture which has no or only low reactivity to the complex metal hydride applied. In these reactions a  $C_{1-4}$  alcohol or pyridine is the solvent of choice. (Similar selective reductions are described in the U.S. patent specifications Nos. 4,423,044 and 4,835,152.)

The nitro group of the new compounds of general formula (V) are reduced to an amino group by hydrazine or hydrazine hydrate in the presence of a catalyst such as palladium, platinum or Raney nickel in a  $C_{1-4}$  alcohol, dioxane, tetrahydrofuran, benzene, dimethylformamide, dimethylacetamide or in a mixture thereof.

According to a preferred embodiment of the process of the present invention the reduction can be carried out in methanol by hydrazine or hydrazine hydrate in the presence of Raney nickel catalyst in a temperature range of 10 to 65 °C (U.S. patent specification No. 4,614,740) but, if desired, the reduction and the removal of the phthaloyl protecting group described in process d) can be performed in the same vessel.

The N-phthaloylamino acids of the general formula (IV) containing a chiral carbon atom, wherein  $R^5$  means a  $C_{1-4}$  alkyl group and n is 1, can be prepared from DL-, L- and/or D- $\alpha$ -amino acids.

The compounds of the general formula (I) of the invention, which contain a basic amino group, wherein  $R^3$  and  $R^4$  mean a hydrogen atom or R and/or  $R^4$  stand for an aminoacyl group, can be transformed to their acid-addition salts by known methods.

The preparation of the compounds of the general formula (II) used as starting materials in the process of the present invention is described in the U. S. patent specification No. 4,614,740, that of the compound of the general formula (III), wherein  $R^4$  stands for a hydrogen atom, in the U. S. patent specification No. 4,835,152, while that of the compound of general formula (IV) is published in the French patent specification No. 85,09793. The compounds of general formula (III), wherein  $R^4$  stands for various acyl groups, are new. The process for their preparation is described herein-after, before Table 10, or they can be synthesized by methods described therein. The preparation of the new starting compounds of the general formula (V) is described in the Examples. The ( $\alpha$ - $\epsilon$ )-amino acid derivatives of general formula (VI) are prepared by methods known from the literature [J. Am. Chem. Soc. 35, 1133 (1913); 41, 845 (1919); Berichte der Deutschen Chemischen Gesellschaft 40, 498, 2649 (1907); 46, 1103, 3159 (1913); 47, 3166 (1914)] or by known methods using the reaction of phthalimide potassium with the required halocarboxylic acid.

The compounds of the general formula (I) prepared by the process of the present invention possess central nervous system (CNS) activity, such as anticonvulsive, muscle-relaxant and neuroprotective effects, which can be shown by pharmacological tests.

In the comparative study 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (U. S. patent specification No. 4,614,740, in the following "reference compound"), having similar structure and efficacy as the com-

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pounds of the invention, was applied as reference compound. As already mentioned in the introduction, this compound proved to be Ames-positive in addition to its valuable pharmacological properties. In opposition to this the compounds of the present invention proved to be negative in the Ames-test.

The pharmacological effects of the compounds of general formula (I) are presented in Tables 1 to 8.

### Narcosis-potentiating effect in mice

The narcosis-potentiating effect was tested with 3 oral doses in 10 mice/dose. The ED<sub>50</sub> value is the dose prolonging the narcosis period induced by 50 mg/kg of i.v. sodium hexobarbital to its twofold value in 50 % of the animals in comparison to the control group treated only with the vehicle. The ED<sub>50</sub> values were calculated by the Litchfield-Wilcoxon method [J. Pharmacol. Exp. Ther. 96, 99 (1949)]. The results are presented in Table 1.

Table 1

Narcosis potentiating effect in mice	
Compound Example No.	ED <sub>50</sub> p.o. mg/kg
Reference compound	7.4
15 (16)	3.6
18	8.8
39	27.5
42	7.9
44	13.5
44	13.5
45	4.9
46	11.5
48	5-8
49	9.5
56	12.5-25
60	4.4
62	5.2
66	24.0
69	15-20
73	4.5
98	5.8
107	6.25-12.5
108	~ 12.5
109	~ 12.5
115	7.7

The data of Table 1 demonstrate that the efficacy of several compounds is similar or significantly superior to that of the reference compound. Compounds of Examples 15 (16), 45, 60, 73 and 98 proved to be especially potent.

### Anticonvulsive effect in mice

The anticonvulsive effect of the compounds was measured by using the electroshock test [Swinyard: J. Pharmacol. Exp. Ther. 106, 319 (1952)], furthermore by using various chemical agents such as pentetrazole [Goodman: J. Pharmacol. Exp. Ther. 108, 168 (1953)], strychnine [Roskovski: J. Pharmacol. Exp. Ther. 129, 75 (1960)], bemegride, nico-

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tine and 4-aminopyridine. The test compounds were orally administered in 3 doses, to 10 male CFLP mic per dose. The results are presented in Table 2.

Table 2

Anticonvulsive effect in mice						
Compound Example No.	ES	Pentetrazole	Strychnine ED <sub>50</sub> p.o. mg/kg	Bemegride	Nicotine	4-AP
Reference compound	38	115	87	73	70	43
15 (16)	12.5	37	>200	16	45	9
18	17.5	29				
39	53	170	>200	>200	>200	29
42	24	33	28	24	155	34
45	27	44	>100	51	30-80	~70
46	20	57	>100	70-80	~100	25-30
48	10.5	35-40				
49	25	53	>100	30-35	45	28
60	24	62				
62	12.5	56		25-50		
66	42	135	~100	>100	100-150	84
69	57	>100				
73	16	62	50-100	49	53	25
98	8.4	19	20	11	19	13.5
107	23.5	120				
108	27	>100				
109	21	>100				
115	17.1	23.9				

ES = electroshock 4-AP = 4-aminopyridine

The above data demonstrate that the anticonvulsive effect of several test compounds (of Examples 15, 42, 45, 46, 73, 98, 107, 108, 109 and 115) is superior to that of the reference compound.

## Muscle-relaxant activity in mice

The muscle-relaxant activity was measured in two tests. In Randall's inclined screen test [J. Pharmacol. Exp. Ther. 129, 163 (1960)] the compounds were applied in 3 i.p. doses to 10 CFLP mice per dose. The results are shown in Table 3.

Table 3

Inclined screen test in mice	
Compound Example No.	ED <sub>50</sub> i.p. mg/kg
Reference compound	47
15 (16)	23.5
18	31
42	42
45	35
48	20.5
49	36
60	150
62	25
66	52
73	27
98	18.0
107	>200
108	>200
109	61
115	16.1

The rotarod test was used to measure muscular tone and motor coordination [Dunham and Miya: J. Am. Pharm. Assoc. 46, 208 (1957)]. The results obtained with the three selected compounds of highest activity and that of the reference compound are presented in Table 4.

Table 4

Rotarod test in mice	
Compound Example No.	ED <sub>50</sub> i.p. mg/kg
Reference compound	24
15 (16)	3.7
42	8.1
98	8.6

Tables 3 and 4 demonstrate that several compounds possess strong muscle-relaxant activity (compounds of Examples 15, 18, 42, 45, 48, 49, 62, 73, 98 and 115).

#### Effect on spinal function

The effect on spinal function was studied with the most active compound (compound of Example 15 or 16) and the reference compound. Table 5 shows the effect on polysynaptic flexor reflexes in cats [Farkas and Kárpáti: Pharm. Res. Comm. 20, S1, 141 (1988)].



Tabl 5

Effect on spinal flexor reflex			
Compound Example No.	Cumulative doses mg/kg, i.v.	Inhibition of flexor reflex in per cent of control	ED <sub>50</sub> mg/kg
Reference compound    15 (16)	0.25	12	0.90 (0.46-1.76)
	0.5	30	
	1.0	57	
	2.0	77	
	0.05	11	(0.19-0.62)
	0.1	19	
	0.2	31	
	0.4	52	
	0.8	77	

The effect of the above compounds on the spinal root potentials in cats was tested in spinally immobilized animals [Farkas et al.: Neuropharmacology 21, 161 (1989)].

The results are presented in Table 6.

Table 6

Effect on spinal root potentials in cats					
Compound Example No.	Inhibition of reflexes in per cent of control				
	Cumulative i.v. doses mg/kg	Monosynaptic reflex	Polysynaptic reflex	Dorsal root reflex	Dorsal root potential
Reference compound	0.5	16	15	0	2
	1.0	27	24	2	4
15 (16)	2.0	47	43	4	4
	0.1	10	8	1	1
	0.2	10	16	3	2
	0.4	32	29	5	4
	0.8	56	51	11	8
	1.4	78	73	14	14

Monosynaptic reflex-inhibiting ED<sub>50</sub> values:

Reference compound: 2.20 (1.02-4.75) mg/kg, i.v.

Compound No. 15 (16): 2.30 (1.06-5.01) mg/kg, i.v.

Polysynaptic reflex-inhibiting ED<sub>50</sub> values:

Reference compound: 0.60 (0.32-1.13) mg/kg, i.v.

Compound No. 15 (16): 0.73 (0.39-1.37) mg/kg, i.v.

## Electrophysiological tests

The inhibitory effects on the field potentials induced by electric stimulation in surviving rat neocortex slices in vitro [Fletcher et al., Br. J. Pharmacology 95, 585 (1988)] are summarized in Table 7.

Table 7

Inhibition of field potentials induced in rat neocortex slices			
Compound Example No.	Concentration $\mu\text{M}$	Inhibition of induced field potentials in % of control	IC <sub>50</sub> $\mu\text{M}$
Reference compound	10	22	30.0
	20	39	
	40	62	
	80	73	
15 (16)	10	30	21.5
	20	47	
	40	69	
	80	82	

The non-NMDA (quisqualate) antagonist effect was tested in rat neocortex slices by using the method of Harrison and Simmonds [Br. J. Pharmacol. 84, 381 (1981)]. In rat neocortex slices the DC-potential changes induced by quisqualate perfusion were dose-dependently inhibited by the reference compound in the concentration range of 10-50  $\mu\text{M}$ . At the concentration defined, the compound of Example 15 (16) proved to be twice as active as the reference compound in inhibiting the response to the 2-minute perfusion with 10  $\mu\text{M}$  of quisqualate. However, both molecules failed to affect the responses induced by NMDA. Accordingly, the compound of Example 15 (16) can be considered to be a selective, non-NMDA but quisqualate-type excitatory amino acid antagonist.

## Acute toxicity in rats

Acute toxicity data obtained in rats are summarized in Table 8.

Table 8

Acute toxicity in rats			
Compound Example No.	Sex	Route of administration	LD <sub>50</sub> mg/kg
15 (16)	Male	i.p.	145 (128-163.1)
	Male	p.o.	>200
	Female	i.p.	140 (122-161)
	Female	p.o.	235 (190-291)
42	Male	i.p.	155 (109.9-218.5)
	Male	p.o.	>600
	Female	i.p.	180 (156.5-207.0)
	Female	p.o.	>600

At toxic dose levels the compounds induced a dose-dependent muscle tone reduction, ataxia, adynamia, and loss of the righting reflex. The cause of mortality was respiratory insufficiency developing within 1 to 2 hours after i.p. administration and within 10 to 20 hours after oral application.

Based on the above pharmacological results, the compounds of general formula (I) according to the invention possess significant anticonvulsive, muscle-relaxant and excitatory amino acid-antagonist (neuroprotective) effects. Thus, they are therapeutically useful for the treatment of epilepsy as well as various diseases connected with spasms of the skeletal musculature and cerebral ischaemia (stroke).

The invention also relates to pharmaceutical compositions containing compounds of general formula (I) or pharmaceutically acceptable acid-addition salts thereof as active ingredients as well as to the preparation of these compositions.

For therapeutical use, the active compounds according to the invention are suitably formulated to pharmaceutical compositions by admixing them with commonly used nontoxic, inert, solid or liquid pharmaceutical carriers and/or auxiliary materials useful for enteral or parenteral administration. As carriers, e.g. water, gelatine, lactose, starch, pectin, magnesium stearate, stearic acid, talc or vegetable oils can be used. As auxiliary materials, e.g. preservatives and wetting as well as emulsifying, dispersing and aromatizing agents and buffers can be employed.

By using the above-mentioned carriers and auxiliary materials, the active agents of the invention may be transformed to the usual pharmaceutical compositions, e.g. to solid compositions (such as tablets, capsules, pills or suppositories) or liquid compositions (such as aqueous or oily solutions, suspensions, emulsions or syrups) as well as to injectable solutions, suspensions or emulsions.

For therapeutical purposes, the daily dose of the compounds of the invention amounts commonly to 0.2-1.5 mg/kg of body weight which is administered daily, optionally divided to several doses.

Based on the above facts, the present invention also provides:

- a method of blocking one or more excitatory amino acid receptors in mammals. This method comprises administering to a mammal in need of such treatment a pharmaceutically effective amount of the general formula (I);
- a method of treating epilepsy in mammals. This method comprises administering to the mammal in need of such treatment an antiepileptic amount of a compound of the general formula (I);
- a method of treating spasms of the skeletal musculature in mammals. This method comprises administering to the mammal in need of such treatment a muscle-relaxing amount of a compound of the general formula (I);
- a method of treating cerebral ischaemia (stroke) in mammals. This method comprises administering to the mammal in need of such treatment a pharmaceutically effective amount of a compound of the general formula (I).

The compounds prepared by the process of the invention were identified by elementary analysis, their purity and structure were controlled and confirmed by thin-layer chromatography, IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and mass spectrometry. The invention is illustrated in detail by the following non-limiting Examples.

#### Example 1

##### 1-(4-Diacetylaminophenyl)-3-acetyl-4-methylene-7,8-methylenedioxy-4,5-dihydro-3H-2,3-benzodiazepine

2.93 g (0.01 mol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were refluxed with 20 ml of acetic anhydride for 6 hours. The solution was evaporated at reduced pressure, the residue was taken up in 2x20 ml of anhydrous ethanol, the solution was repeatedly evaporated and the resulting residue of 4.55 g was submitted to column chromatography (adsorbent: Kieselgel 60, eluant: ethyl acetate - benzene 4:1). The raw product was triturated with 20 ml of hot isopropanol to yield 1.44 g (34.4 %) of the aimed product, m.p. 240-245 °C (slight decomp.).  
 $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_5 = 419.445$

#### Example 2

##### 1-(4-Formylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

3.0 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were dissolved in 160 ml of dichloromethane and first 2.75 g (13.3 mmol) of dicyclohexylcarbodiimide, then 0.51 ml (13.3 mmol) of 100 % formic acid were added and the reaction mixture was stirred for 2 hours at room temperature. The precipitated N,N'-dicyclohexylurea was filtered, the filtrate was extracted with 2x30 ml of 10 % aqueous sodium carbonate solution, then with 2x30 ml of distilled water, the organic layer was dried and evaporated at reduced pressure. The residue was dissolved in ethyl acetate, filtered and evaporated under reduced pressure. The resulting raw product was recrystallized from 20 ml of 50 % ethanol to yield 2.93 g (89.3 %) of the aimed product, m.p. 152-154 °C (slight decomp.).  
 $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3 = 321.342$

## Examples 3 to 7

The compounds of Examples 3 to 7 were prepared by the process described in Example 2.

## 5 Example 3

1-(4-Cyanoacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

$C_{20}H_{16}N_4O_3 = 360.380$ , m.p.: 241-243 °C (decomp.).

10

## Example 4

1-(4-Methoxyacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

15  $C_{20}H_{19}N_3O_4 = 365.396$ , m.p.: 203-205 °C

## Example 5

1-(4-Valerylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

20

$C_{22}H_{23}N_3O_3 = 377.450$ , m.p.: 217-219 °C (decomp.).

## Example 6

25 1-(4-Phenylacetylaminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine

$C_{25}H_{21}N_3O_3 = 411.467$ , m.p.: 245-247 °C (decomp.).

## Example 7

30

1-(4-Cyclopropanecarbonylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

$C_{21}H_{19}N_3O_3 = 361.407$ , m.p.: 260-262 °C (decomp.).

## 35 Example 8

1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

40 10 g (34 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were stirred for 3 hours with 100 ml of acetic anhydride. The crystals formed were filtered, washed with 5x10 ml of anhydrous ethanol and dried, yielding 9.2 g of raw product, m.p. 252-254 °C (decomp.). This product was treated with 45 ml of hot 99.5 % ethanol. After cooling the crystals were filtered, washed with 3x10 ml of ethanol and dried to give 8.68 g (76.1 %) of the aimed product, m.p.: 256-258 °C (decomp.).

$C_{19}H_{17}N_3O_3 = 335.369$

45

## Example 9

1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

50  $C_{20}H_{19}N_3O_3 = 349.396$ , m.p.: 228-230 °C (decomp.).

It was prepared by the process described in Example 8.

## Example 10

55 1-(4-Pivaloylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

1.56 ml (11.2 mmol) of triethylamine and 1.38 ml (11.2 mmol) of pivaloyl chloride were added to a solution of 3 g (10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 160 ml of dichloromethane and the reaction mixture was stirred at 25 °C for one hour. The precipitate formed was filtered, washed with 3x5 ml of

dichloromethane, then with 3x20 ml of water and dried to yield 1.59 g of pure product, m.p. 225-227 °C (decomp.). The other portion of the product was isolated from the organic phase. The filtrate was extracted with 3x20 ml of water, then with 3x15 ml of 4 % aqueous sodium hydroxide solution, finally with 2x30 ml of water. The organic layer was subsequently dried and evaporated under reduced pressure. The crystalline residue was combined with the former product of 1.59 g and suspended in 20 ml of hot ethanol. The product was filtered after cooling, washed with 3x3 ml of ethanol and dried to yield 3.38 g (87.8 %) of the pure product, m.p.: 225-227 °C (decomp.).

$C_{22}H_{23}N_3O_3 = 377.450$

#### Example 11

##### 1-(4-Benzoylamino)phenyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

1.0 ml (15 mmol) of benzoyl chloride and 2.1 ml (15 mmol) of triethylamine were added to a solution of 4 g (13.6 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane and the reaction mixture was stirred at 25 °C for 24 hours. The solution was extracted with 3x30 ml of water, 3x20 ml of a 4 % aqueous sodium hydroxide solution and finally with 2x30 ml of distilled water. The organic layer was dried, evaporated under reduced pressure, then the crystalline residue was treated with 20 ml of hot ethanol to obtain 3.97 g of raw product, m.p. 242-243 °C. This raw product was repeatedly treated with 20 ml of hot ethanol, next day it was filtered at 0-5 °C, washed with 3x3 ml of ethanol and dried at 100 °C to yield 3.85 g (71.3 %) of the pure aimed product, m.p. 246-247 °C (decomp.).

$C_{24}H_{19}N_3O_3 = 397.40$

#### Example 12

##### 1-(4-Palmitoylamino)phenyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

By following the process described in Example 11, with recrystallization of the raw product from 50 % ethanol, the pure aimed product was obtained, m.p. 138-140 °C.

$C_{33}H_{45}N_3O_3 = 531.747$

#### Example 13

##### 1-(4-Phenylcarbamoylamino)phenyl-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

0.22 ml (2.04 mmol) of phenyl isocyanate was added to a solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 4 ml of dimethylformamide and the reaction mixture was stirred at 25 °C for one hour. Then it was diluted with 20 ml of diethyl ether and filtered at 5 °C. The crystals were washed with 2x5 ml of diethyl ether and dried at 60-100 °C. The resulting 0.70 g of raw product, m.p. 239-240 °C (sintering at 180 °C) was refluxed in 15 ml of ethanol, filtered after cooling, washed with 3x1 ml of ethanol and dried at 100 °C to yield 0.55 g (78.6 %) of the aimed product, m.p. 240-241 °C (decomp.).

$C_{24}H_{20}N_4O_3 = 412.456$

#### Example 14

##### 1-[4-(4-Carboxybutyrylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

A solution of 0.50 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 30 ml of anhydrous dichloromethane was stirred with 0.18 g (1.87 mmol) of glutaric acid anhydride at 20-25 °C for 6 hours. Next day the crystals formed were filtered at 0-5 °C, washed with 3x2 ml of dichloromethane and dried at 60-80 °C to give 0.60 g (87.0 %) of the pure aimed product, m.p. 225-227 °C (decomp.).

$C_{22}H_{21}N_3O_5 = 407.434$

#### Example 15

##### 1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of 3.58 g (12.1 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 100 ml of chloroform first 1.68 ml (12.1 mmol) of triethylamine, then under constant ice-cooling and stirring 1.15 ml (12.1 mmol) of acetic anhydride were added. Stirring was continued for additional 2 hours, then the solution was

extracted with 3x100 ml of water, the organic layer was dried and evaporated under reduced pressure. The crystalline residue was recrystallized from 40 ml of isopropanol to obtain 3.50 g (85.7 %) of the aimed product, m.p. 220-222 °C. After repeated recrystallization the m.p. increased to 223-225 °C.

$C_{19}H_{19}N_3O_3 = 337.385$

Hydrochloride:  $(C_{19}H_{20}N_3O_3)Cl = 373.850$ , m.p.: 248-252 °C (decomp.).

#### Example 16

##### 1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a suspension of 1.91 g (5.37 mmol) of 1-(4-nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (product of Example 27) in 40 ml of methanol about 0.2 g of Raney nickel catalyst and 1.4 ml (28 mmol) of 100 % hydrazine hydrate were added, then the reaction mixture was stirred at 20-25 °C for one hour. The starting nitro derivative was dissolved within 10-20 minutes. After filtering the filtrate was evaporated under reduced pressure, the white crystalline residue was washed with 30 ml of distilled water onto a filter, it was washed with 3x10 ml of distilled water and dried at 100 °C to give 1.50 g of a raw product, m.p. 218-220 °C. This raw product was purified by treating with 12 ml of hot isopropanol. After cooling it was filtered at 5 °C, washed with 3x1 ml of isopropanol and dried at 100 °C to yield 1.40 g (77.35 %) of a white crystalline powder, m.p. 221-223 °C. On the basis of analyses and spectra it was identical to the product of Example 15 obtained by a different process.

#### Example 17 to 25

The process described in Example 16 was followed for preparing other 1-(4-aminophenyl)-3-R-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepines of the general formula (I). The data of the products prepared are presented in Table 9.

Table 9

Products of the general formula (I) wherein $R_2 = CH_3$ and $R_1 = R_3 = R_4 = H$		
Example No.	R	M.p. °C
17	Trifluoroacetyl	215-217
18	Propionyl	211-213
19	Valeryl	178-180
20	Pivaloyl	233-235 (d)
21	Benzoyl	220-222
22	Phenylacetyl	220-221
23	Cyclopropylcarbonyl	138-140
24	Cyanoacetyl	123-126
25	Methoxyacetyl	125-127

(d) = decomposition

The new nitro compounds of the general formula (V), wherein R = H or acyl group, used in the preparation of products of Examples 16 to 25, can be prepared by processes described in Examples 26 to 36.

#### Example 26

##### 1-(4-Nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a suspension of 5.0 g (15.5 mmol) of the known 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (French patent specification No. 85,09793) in 380 ml of ethanol first 22.5 ml (0.278 mol) of concentrated hydrochloric acid were added at constant stirring whereupon a solution was formed within a few minutes, then 11.5 g

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(0.3 mole) of sodium borohydride were charged into the solution portionwise during 30 minutes. Stirring was continued for 15 minutes, then the orange-coloured precipitate formed was filtered and extracted on the filter with 4x30 ml of chloroform. The combined chloroform filtrate was evaporated under reduced pressure, the crystalline residue was brought to a filter with 200 ml of distilled water, then washed with 3x20 ml of distilled water and dried at 80-100 °C to yield 4.90 g (97.2 %) of the aimed product, m.p.: 162-164 °C.

$C_{17}H_{15}N_3O_4 = 325.331$

### Example 27

#### 1-(4-Nitrophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A 2.0 g (6.15 mmol) portion of the product of Example 26 was stirred with 10 ml of acetic anhydride at 25 °C for 3 hours then 50 ml of distilled water were added and the stirring was continued for one hour. The yellow precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 80-100 °C to obtain 2.6 g of raw product. After recrystallization from 10 ml of ethanol 1.94 g (85.8 %) of the aimed product were obtained, m.p.: 140-142 °C.

$C_{19}H_{17}N_3O_5 = 367.369$

### Example 28

#### 1-(4-Nitrophenyl)-3-trifluoroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

To a solution of a 1.5 g (4.61 mmol) portion of the product of Example 26 in 30 ml of anhydrous dichloromethane 0.75 ml (5.3 mmol) of trifluoroacetic acid anhydride and 0.75 ml (5.3 mmol) of triethylamine were added and the reaction mixture was stirred at 25 °C for 3 hours. Subsequently, the mixture was extracted with 3x20 ml of water and the organic layer was dried and evaporated under reduced pressure. The crystalline residue was treated with 15 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried at 80-100 °C to yield 1.84 g (94.85 %) of the aimed compound as a bright yellow crystalline product, m.p.: 165-167 °C (decomp.).

$C_{19}H_{14}F_3N_3O_5 = 421.339$

### Example 29

#### 1-(4-Nitrophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

A 1.54 g (4.7 mmol) portion of the product of Example 26 was stirred with 8 ml of propionic acid anhydride at 25 °C for 3 hours, then 30 ml of diethyl ether were added and the solution was kept at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x8 ml of diethyl ether and dried to yield 1.32 g (73.7 %) of the aimed compound as a light yellow product, m.p.: 189-190 °C.

$C_{20}H_{19}N_3O_5 = 381.396$

### Example 30

#### 1-(4-Nitrophenyl)-3-valeryl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

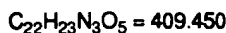
To a solution of a 2.5 g (7.68 mmol) portion of the product of Example 26 in 40 ml of anhydrous dichloromethane 4.75 g (23 mmol) of dicyclohexylcarbodiimide and 2.88 g (23 mmol) of n-valeric acid were added and the reaction mixture was maintained at 25 °C under intermittent stirring for 24 hours. Then the N,N'-dicyclohexylurea formed as by-product was filtered, the filtrate was evaporated under reduced pressure, the residue was mixed with 2x40 ml of distilled water, decanted and the wet product was left to solidify under 50 ml of 50 % ethanol. The solid compound was filtered, washed with 2x10 ml of 50 % ethanol and dried at 80 °C. The raw product obtained was recrystallized from 24 ml of ethanol and the crystals were dried at 100 °C to yield 2.20 g (70 %) of the aimed product as a yellow powder, m.p.: 145-147 °C.

$C_{22}H_{23}N_3O_5 = 409.450$

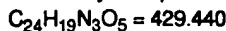
### Example 31

#### 1-(4-Nitrophenyl)-3-pivaloyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

By following the process described in Example 28 but applying pivaloyl chloride instead of trifluoroacetic acid anhydride 1.68 g (89.4 %) of the aimed product were obtained, m.p.: 164-166 °C.

**Example 32**5 **1-(4-Nitrophenyl)-3-benzoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

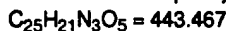
By following the process described in Example 31 but using benzoyl chloride as acyl chloride, 1.72 g (86.9 %) of an ochre yellow product were obtained, m.p.: 222-224 °C (decomp.).



10

**Example 33**11 **1-(4-Nitrophenyl)-3-phenylacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

15 By following the process described in Example 30 but using 50 % of the calculated molar amount of dicyclohexylcarbodiimide and phenylacetic acid, a bright yellow product was obtained, m.p.: 193-195 °C.

**Examples 34 to 36**

20

The products of Examples 34 to 36 were obtained by following the process described in Example 33 and using the respective acid components.

**Example 34**

25

**1-(4-Nitrophenyl)-3-cyclopropanecarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 225-228 °C (decomp.).



30

**Example 35****1-(4-Nitrophenyl)-3-cyanoacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

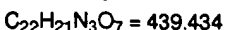
35 M.p.: 185-188 °C

**Example 36**40 **1-(4-Nitrophenyl)-3-methoxyacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 187-189 °C

45 **Example 37****1-(4-Nitrophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

50 By using the product of Example 26 as starting material and performing the acylation according to Example 14 with glutaric acid anhydride, finally recrystallizing the raw product from ethanol the pure aimed product was obtained, m.p.: 148-150 °C.

**Example 38**

55

**1-(4-Aminophenyl)-3-phenylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

To a solution of 0.70 g (2.3 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 10 ml of anhydrous benzene 0.24 ml (2.3 mmol) of phenyl isocyanate was added and the reaction mixture



was refluxed for one hour. Thereafter the solution was evaporated under reduced pressure and the amorphous residue was mixed with 20 ml of hot 50 % ethanol. The suspension was cooled to 0 °C and filtered to yield 0.76 g of a raw product, m.p. 190-200 °C. After recrystallization from 99.5% ethanol and trituration with ethyl acetate the aimed compound melts at 207-209 °C.

5  $C_{24}H_{22}N_4O_3 = 414.472$

The preparation of the starting material of this example was described in the Hungarian patent specification No. 198,494. However, the compound may also be prepared by a new method according to the process of Example 16, by using the compound of Example 26 as starting material to give excellent yields (84 %). The raw product may be recrystallized from 50 % ethanol, m.p.: 118-120 °C.

10

#### Example 39

##### 1-(4-Diacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

15 2.0 g (6.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were refluxed with 40 ml of acetic anhydride for 3 hours, then it was evaporated to dryness under reduced pressure. The crystalline residue was transferred with 25 ml of water to a filter and washed with 5x3 ml of water. After drying 2.79 g of the raw triacetyl derivative were obtained. After washing with 20 ml of isopropanol and drying at 100 °C 2.39 g (84.6 %) of the pure aimed product were obtained, m.p. 224-227 °C.

20  $C_{23}H_{23}N_3O_5 = 421.461$

#### Example 40

##### N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-methylurea

25 0.70 g (2 mmol) of the product of Example 15 was dissolved in benzene dehydrated over calcium hydride, 0.3 ml (5 mmol) of methyl isocyanate was added and the reaction mixture was stirred at 50 °C for 4 hours. The crystals formed after cooling were filtered, washed with 3x3 ml of benzene, then triturated with 20 ml of hot benzene. The hot mixture was filtered, the precipitate was washed with 3x3 ml of benzene and dried to give 0.65 g (79.6 %) of the aimed product, m.p.: 168-170 °C (decomp.).

30  $C_{21}H_{22}N_4O_4 = 394.439$

#### Example 41

##### N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-phenylurea

By following the process described in Example 40 but using phenyl isocyanate instead of methyl isocyanate, refluxing the reaction mixture for 10 hours, evaporating it under reduced pressure, then suspending the residue first in 50 ml of diethyl ether and then in 15 ml of ethyl acetate, 0.69 g (75.7 %) of the aimed product was obtained, m.p.: 184-186 °C (decomp.).

40  $C_{26}H_{24}N_4O_4 = 456.510$

#### Example 42

##### 1-(4-Acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

45 1.3 g (4.4 mmol) of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were stirred at 20-25 °C with 5 ml of acetic anhydride for one hour, then the yellow solution was poured into 100 g of ice-water and stirred until the decomposition of the excess anhydride became complete. The precipitate formed was filtered, washed with 3x10 ml of distilled water and dried to give 1.6 g of raw product. After recrystallization from 20 ml of benzene 1.50 g (89.85 %) of the aimed product were obtained, m.p.: 158-160 °C (decomp.).

50  $C_{21}H_{21}N_3O_4 = 379.423$

#### Example 43

##### 1-(4-Formylaminophenyl)-3-formyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

55 T 6.0 ml (0.104 mol) of acetic anhydride 3.0 ml (0.08 mol) of 100 % formic acid were added dropwise at 0 °C during 5 minutes while constant stirring. The stirring was continued at 50 °C for 15 minutes. Thereafter 1 g (3.3 mmol) of 1-(4-

aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine was added to the thus-prepared mixed anhydride. The reaction mixture was stirred at 25 °C for 1.5 hours, then poured into ice-water, the precipitate formed was filtered, washed with 4x5 ml of distilled water and dried at 80 °C to give 0.80 g of raw product. After crystallization from 3 ml of ethyl acetate 0.65 g (56.2 %) of the aimed product was obtained, m.p.: 193-195 °C.

$C_{19}H_{17}N_3O_4 = 351.369$

#### Example 44

##### 1-(4-Trifluoroacetylaminophenyl)-3-trifluoroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.48 g (5 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine were dissolved in 30 ml of anhydrous chloroform, then 2.1 ml (15 mmol) of triethylamine and at 20-25 °C 2.12 ml (15 mmol) of trifluoroacetic anhydride were added and the reaction mixture was stirred for 2.5 hours, then extracted first with 2x30 ml of water and thereafter with 20 ml of 5 % hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate, evaporated under reduced pressure and the amorphous residue was recrystallized from 10 ml of 70 % ethanol to give 1.41 g (57.9 %) of the aimed diacyl derivative, m.p. 177-178 °C.

$C_{21}H_{15}F_6N_3O_4 = 487.363$

#### Example 45

##### 1-(4-Propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

The process described in Example 44 was followed, except that 11.2 mmol of both triethylamine and propionic acid anhydride were used and the crystalline residue was recrystallized first from 15 ml of 50 % ethanol, then from 11.5 ml of 99 % ethanol to give 2.48 g (60.9 %) of the aimed product, m.p.: 152-154 °C.

$C_{23}H_{25}N_3O_4 = 407.477$

#### Examples 46 to 65

Other diacyl derivatives of the general formula (I), wherein R = acyl group,  $R^1 = R^3 = H$ ,  $R^2 = CH_3$  and  $R^4 =$  acyl group, where R and  $R^4$  are the same or different, are presented in Table 10. These compounds were prepared partly from compounds of the general formula (III), wherein  $R = R^1 = R^3 = H$  and  $R^4 =$  acyl group; and partly from new compounds of the general formula (I), wherein R = acyl group,  $R^1 = R^3 = R^4 = H$  and  $R^2 = CH_3$ , according to processes defined in the preceding examples.

The preparation of starting substances of general formula (III), wherein  $R = R^1 = R^3 = H$  and  $R^4 =$  acyl group is illustrated in detail below on the derivative bearing acetyl group as  $R^4$ :

##### 1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

#### Method A)

To a solution containing 6.0 g (20 mmol) 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 30 ml of ethyl acetate 1.38 ml (21 mmol) of methanesulfonic acid were added. The crystalline precipitate was filtered and washed with 5 x 5 ml of ethyl acetate. The dry weight of the product was 7.37 g, m.p.: it sintered above 190 °C and weakly decomposed at 210-212 °C. The thus-obtained methanesulfonate salt of the starting substance was acetylated as follows:

7.37 g of the powdered salt were suspended in 110 ml of acetic anhydride, the suspension was stirred at room temperature for 2 hours, then the crystalline precipitate was filtered, washed with 5 x 10 ml of ethyl acetate and dried to give 6.54 g of methanesulfonate salt of the target compound, m.p. 240-241 °C (with decomposition).

The base was liberated from the methanesulfonate salt of the target compound e.g. in the following way: 6.54 g of salt were dissolved in 90 ml of water, the solution was clarified by charcoal, then 3.6 g of sodium hydrogen carbonate were portionwise added to the clear solution. The precipitate was filtered, washed with 5 x 10 ml of water and dried to obtain 5.54 g of crude product. After recrystallization from 130 ml of isopropanol, 3.11 g (yield 46 %) of product were obtained, m.p.: 221-223 °C (weak decomposition), the melting point of which increased to 223-225 °C after digesting with 15 ml of hot benzene.

$C_{19}H_{19}N_3O_3 = 337.385$

The hydrochloride salt decomposed at 262-264 °C.

## Method B)

After dissolving 15.0 g (44.7 mmol) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 150 ml of pyridine under mild heating, 10.2 g (0.269 mol) of sodium borohydride were added and the mixture was stirred on an oil bath at a temperature of 100 °C for 5 hours. Then the reaction mixture was cooled to about 25 °C, 150 ml of water were dropwise added under continuous stirring during 20 minutes, thereafter a mixture containing 180 ml of concentrated hydrochloric acid and 265 ml of water was added while cooling with ice-water. A yellowish suspension was formed. The precipitate was filtered, washed with 5 x 20 ml of water and dried to yield 15.2 g of salt, m.p. above 250 °C. In order to liberate the base, this salt was suspended in 150 ml of 50 % ethanol and then 5.7 g of sodium hydrogen carbonate were portionwise added while stirring. The thus-formed suspension was filtered after 30 minutes, washed successively with 3 x 10 ml of 50 % ethanol, 5 x 20 ml of water, finally with 20 ml of 50 % ethanol and dried to obtain 10.95 g of a crude product, m.p.: 218-220 °C (weak decomposition). After digesting this crude product with 50 ml of hot isopropanol and then with 100 ml of hot 99.5 % ethanol, 8.63 g (57.2 %) of the aimed compound were obtained, m.p.: 220-222 °C (weak decomposition).

Physical characteristics of other 1-(4-acylamino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3 -benzodiazepine are as follows:

R <sup>4</sup> -Analogue	M.p. °C
Propionyl	237-239
Benzoyl	247-248 (decomp.)
Phenylacetyl	213-215 (decomp.)
Pivaloyl	132-135 (decomp.)

Table 10

Compounds of the general formula (I), wherein $R^1 = R^3 = H$ , $R^2 = CH_3$ , R and $R^4$ are acyl groups					
Example No.	R	$R^4$	Starting material Example No.	Process of Example No.	M.p. °C
46	COCH <sub>3</sub>	CHO	15 (16)	2, 30	142-144
47	COCF <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	28, 44	212-214
48	COCH <sub>3</sub>	COC <sub>2</sub> H <sub>5</sub>	15 (16)	28, 44	155-157
49	COC <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	28, 44	168-170
50	COCH <sub>3</sub>	CO-C(CH <sub>3</sub> ) <sub>3</sub>	15 (16)	31	201-203
51	CO-C(CH <sub>3</sub> ) <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	31	138-140
52	COCH <sub>3</sub>	CO-CH <sub>2</sub> -OCH <sub>3</sub>	15 (16)	2, 30	118-120
53	CO-CH <sub>2</sub> -OCH <sub>3</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	2, 30	136-138 (d)
54	COCH <sub>3</sub>	CO-CH <sub>2</sub> -CN	15 (16)	2, 30	149-151 (d)
55	CO-CH <sub>2</sub> -CN	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	2, 30	128-130 (d)
56	CO-C <sub>6</sub> H <sub>5</sub>	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	31	154-156
57	COCH <sub>3</sub>	CO-C <sub>6</sub> H <sub>5</sub>	15 (16)	31	214-216
58	CO-(CH <sub>2</sub> ) <sub>3</sub> -COOH	COCH <sub>3</sub>	(III), $R^4 = COCH_3$	14	172-174
59	COCH <sub>3</sub>	CO-(CH <sub>2</sub> ) <sub>3</sub> -COOH	15 (16)	14	210-212 (d)
60	CHO	COC <sub>2</sub> H <sub>5</sub>	(III), $R^4 = COC_2H_5$	2	185-187
61	CHO	CO-C(CH <sub>3</sub> ) <sub>3</sub>	(III), $R^4 = CO-C(CH_3)_3$	2	220-221 (d)
62	COCH <sub>3</sub>	COCF <sub>3</sub>	15 (16)	28	150-152 (d)
63	CHO	CO-C <sub>6</sub> H <sub>5</sub>	(III), $R^4 = CO-C_6H_5$	2	202-203 (d)
64	COCH <sub>3</sub>	CO-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	(III), $R^4 = CO-CH_2-C_6H_5$	2	135-137
65	COC <sub>2</sub> H <sub>5</sub>	CHO	18	2	140-141 (d)

(d) = decomposition

**Example 66****1-(4-Glycylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

To a suspension of 2.89 g (5.97 mmol) of 1-(4-phthaloylglycylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (Example 79) in 50 ml of methanol 0.6 ml (11.9 mmol) of 100 % hydrazine hydrate was added and the mixture was refluxed for 2 hours. The reaction mixture was cooled, evaporated under reduced pressure, the partially crystalline residue was mixed with 40 ml of dichloromethane, filtered and the by-product was washed with 2x10 ml of dichloromethane. The solution was extracted with 3x15 ml of 5 % hydrochloric acid, the aqueous layer was made alkaline with 24 ml of aqueous 10 % sodium hydroxide, the precipitate formed was filtered, washed with 3x10 ml of distilled water and dried at 100 °C to obtain 1.67 g of raw product. After recrystallization from 73 ml of ethanol 1.50 g (71.8 %) of the aimed product were obtained, m.p.: 223-225 °C.

C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub> = 350.385**Examples 67 to 78**

Other compounds of the general formula (I), wherein  $R^2 = CH_3$ ,  $R^3 = H$ , and some of their acid addition salts, prepared by the process of Example 66, are presented in Table 11. The salts were prepared by known methods.

Table 11

Example No.	R	R <sup>1</sup>	R <sup>4</sup>	Example No. of starting	M.p. °C (salt) material
67	-	-	CO-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	80	198-200 (d)
68	-	-	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	81	155-157 (d)
69	-	-	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	68	217-219 (d) (H-Fu)
70	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	H	82	150-155
71	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	H	70	190-193 (d) (H-Fu)
72	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	H	H	84	193-195 (H-Fu 210-213 (d))
73	COCH <sub>3</sub>	H	CO-CH <sub>2</sub> -NH <sub>2</sub>	88	210-211 (d) (HCl) [base 230-232 (d)]
74	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	COCH <sub>3</sub>	89	210-212 (d)
75	CO-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	H	COCH <sub>3</sub>	90	154-156 (d) (Fu)
76	(H-Fu), COCH <sub>3</sub>	H	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	91	222-223 (d) (H-Fu)
77	DL-CO-CH(CH <sub>3</sub> )-NH <sub>2</sub>	H	COCH <sub>3</sub>	92	218-220 (d)
78	CO-CH <sub>2</sub> -NH <sub>2</sub>	H	CO-CH <sub>2</sub> -NH <sub>2</sub>	93	202-204 (d)

Notes:  
H-Fu = hydrogen fumarate (H-fumarate),  
Fu = fumarate  
The products of Examples 70 to 72 were prepared from the corresponding starting substances in two steps, by following first Example 66 and then Example 16.

**Example 79****1-[4-(N-Phthaloylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

To a solution of 2.0 g (6.88 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane 1.84 g (8.94 mmol) of dicyclohexylcarbodiimide and 1.84 g (8.94 mmol) of powdered phthalimidoacetic acid were added and the reaction mixture was stirred at 25 °C for 8 hours, then left to stand at 0-5 °C overnight. The precipitate formed was filtered, washed with 3x3 ml of dichloromethane and dried at 60-80 °C to result in 5 g of a product consisting of a mixture of the target product and N,N'-dicyclohexylurea, a by-product. This mixture was purified by refluxing with 210 ml of ethanol for 30 minutes, filtering the hot mixture and washing with 2x10 ml of hot ethanol, thereafter drying at 100 °C to obtain 2.42 g (73.3 %) of the aimed product, m.p.: 266-268 °C (decomp.).

$C_{27}H_{20}N_4O_5 = 480.489$

**Example 80****1-[4-(N-Phthaloyl-γ-aminobutyrylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

By following the process described in Example 79 but using γ-phthalimidobutyric acid, 3.8 g of a mixture were obtained, which was combined with the dichloromethane mother liquor extracted previously with 2x40 ml of a 10 % aqueous sodium carbonate solution. After evaporating under reduced pressure the residue was submitted to column chromatography [adsorbent: Kieselgel 60 (0.063-2 mm), eluent: ethyl acetate:methanol 4:1]. The evaporation residue was triturated with 10 ml of hot ethanol, cooled, filtered, washed with 3x1 ml of ethanol and dried to give 3.12 g (90 %) of the aimed product, m.p.: 233-235 °C (decomp.).

$C_{29}H_{24}N_4O_5 = 508.543$

**Example 81****1-[4-(M-Phthaloyl-DL-alanylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

5 The process described in Example 79 was followed, except that N-phthaloyl-DL-alanine (DL-2-phthalimido-propionic acid) was used. After filtering the slight precipitate formed the filtrate was evaporated, the residue was mixed with 15 ml of dichloromethane, carefully filtered and the clear solution obtained was repeatedly evaporated. The purification of the residue was achieved by refluxing it with 60 ml of ethyl acetate. Crystal formation was already started in the hot solution. The crystals were filtered at 0-5 °C, the nearly white crystal powder was washed with 3x3 ml of ethyl acetate  
 10 and dried at 100 °C to give 2.75 g (80.95 %) of the aimed product, m.p.: 243-245 °C (decomp.).  
 $C_{28}H_{22}N_4O_5 = 494.516$

**Example 82****15 1-(4-Nitrophenyl)-3-glycyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

The process described in Example 66 was followed by using the compound prepared according to Example 85 as starting material, but the dichloromethane solution was extracted only with 3x20 ml of distilled water and the organic layer was evaporated under reduced pressure. The crystalline residue was purified by suspending it in 7 ml of ethanol  
 20 to give the pure aimed product in a yield of 86.1 %, m.p.: 201-203 °C (decomp.).  
 $C_{19}H_{18}N_4O_5 = 382.385$

**Example 83****25 1-(4-Nitrophenyl)-3-(γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

By following the process described in Example 82 and using the compound prepared according to Example 86 as starting material, a product containing crystal solvent was obtained in a yield of 89.4 %, m.p. 110-112 °C (recrystallized from 50 % ethanol).  
 30  $C_{21}H_{22}N_4O_5 = 410.439$

**Example 84****35 1-(4-Nitrophenyl)-3-(DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

By following the process described in Example 82 and using the compound prepared according to Example 87 the aimed compound was obtained, m.p. 220-221 °C (decomp.).  
 $C_{20}H_{20}N_4O_5 = 396.412$

**40 Examples 85 to 87**

The new intermediates employed in Examples 82 to 84 as starting materials were prepared from the compound prepared according to Example 26 by the process of Example 81.

**45 Example 85****1-(4-Nitrophenyl)-3-(N-phthaloylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

Yield: 93.3 %, m.p.: 173-174 °C (decomp.).  
 50  $C_{27}H_{20}N_4O_7 = 512.489$

**Example 86****55 1-(4-Nitrophenyl)-3-(N-phthaloyl-γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

M.p.: 218-220 °C  
 $C_{29}H_{24}N_4O_7 = 540.543$

## Example 87

1-(4-Nitrophenyl)-3-(N-phthaloyl-DL-alanyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

M.p.: 210-212 °C

 $C_{28}H_{22}N_4O_7 = 526.516$ 

## Example 88 to 94

The intermediates of the general formula (I), wherein R and/or R<sup>4</sup> represent(s) C<sub>1-6</sub> acyl group(s) substituted by a phthalimido group, are required for the preparation of compounds obtained by using the processes of Examples 73 to 78 and summarized in Table 12. They were prepared from the compound of Example 15 (16) or from a compound of the general formula (III), wherein R<sub>4</sub> is hydrogen (see U.S. patent specification No. 4,835,152) or from 1-(4-acetylamino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine described hereinabove (before Table 10) by following the process of Example 81.

As a matter of course, in Example 93 a twofold amount of phthaloylglycine and dicyclohexylcarbodiimide have to be used. Thus, Table 12 lists new compounds of the general formula (I), wherein R and R<sup>4</sup> are acyl groups, R<sup>1</sup> = R<sup>3</sup> = H and R<sup>2</sup> = CH<sub>3</sub>.

Table 12

Example No.	R	R <sup>4</sup>	M.p. °C
88	COCH <sub>3</sub>	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	314-316 (d)
89	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	204-206 (d)
90	CO-(CH <sub>2</sub> ) <sub>3</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	150-152
91	COCH <sub>3</sub>	DL-CO-CH(CH <sub>3</sub> )-N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	264-266 (d)
92	DL-CO-CH(CH <sub>3</sub> )-N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	COCH <sub>3</sub>	245-248
93	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO-CH <sub>2</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	230-232 (d)
94	COCH <sub>3</sub>	CO-(CH <sub>2</sub> ) <sub>3</sub> -N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	173-175
(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> = phthaloyl; N(CO) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> = phthalimido;			

(d) = decomposition

## Example 95

1-(4-Aminophenyl)-3-(γ-aminobutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate

It was prepared from the compound of Example 83 by following Example 16, m.p.: 150-152 °C (decomp.)

 $[C_{29}H_{25}N_4O_3] \cdot C_4H_3O_4 = 496.531$ 

## Example 96

1-(4-Aminophenyl)-3-(4-carboxybutyryl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrochloride

It was obtained from the compound of Example 37, according to Example 16, m.p.: 224-226 °C (decomp.).

 $[C_{22}H_{24}N_3O_5]Cl = 445.915$

**Example 97****1-(4-Trifluoroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

It was prepared by following Example 2, m.p.: 258-260 °C (decomp.).

$C_{19}H_{14}F_3N_3O_3 = 389.339$

**Example 98****1-(4-Aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-nitrophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to Example 16, m.p. 199-201 °C.

$C_{19}H_{20}N_4O_3 = 352.401$

Hydrochloride m.p. 219-221 °C (decomp.).

$[C_{19}H_{21}N_4O_3]Cl = 388.866$

The starting nitro compound was prepared as follows:

1.1 ml (18.4 mmol) of methyl isocyanate were added to 3.0 g (9.22 mmol) of 1-(4-nitrophenyl)-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 26) dissolved in 60 ml of dichloromethane and stirred for 24 hours, then evaporated under reduced pressure. The crystalline residue was triturated with 30 ml of hot ethanol at 80 to 100 °C to obtain 3.35 g (95 %) of the lemon-yellow aimed product, m.p.: 238-240 °C (decomp.).

$C_{19}H_{18}N_4O_5 = 382.385$

**Example 99****1-(4-Aminophenyl)-3-(1-pyrrolidinoacetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was obtained from 1-(4-nitrophenyl)-3-(1-pyrrolidino-acetyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by following Example 16, m.p.: 212-214 °C.

$C_{23}H_{26}N_4O_3 = 406.493$

The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 116) according to Example 102, m.p.: 189-190 °C (decomp.).

$C_{23}H_{24}N_4O_5 = 436.477$

**Example 100****1-(4-Aminophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate**

It was prepared from 1-(4-nitrophenyl)-3-(N,N-dimethylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to Example 16, m.p.: 202-204 °C (decomp.).

$[C_{21}H_{25}N_4O_3]C_4H_3O_4 = 496.531$

The starting substance was obtained from 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine according to the process described in Example 103, m.p.: 158-160 °C.

$C_{21}H_{22}N_4O_5 = 410.439$

**Example 101****1-(4-Chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

It was prepared according to Example 2, except that chloroacetic acid was used, m.p.: 209-214 °C (carbonization).

$C_{19}H_{16}ClN_3O_3 = 369.818$

**Example 102****1-[4-(1-Pyrrolidinoacetyl-amino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

0.71 ml (8.53 mmol) of pyrrolidine was added to a suspension of 1.5 g (406 mmol) of 1-(4-chloroacetyl-aminophenyl)-4-methyl-7,8-methyl nedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol and the reaction mixture was refluxed for



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4 hours, then evaporated under reduced pressure. The residue was treated with water to give a rough product (1.49 g), m.p.: 186-188 °C. After recrystallization from 12 ml of ethanol 1.22 g (74.4 %) of the aimed product were obtained, m.p.: 210-212 °C.

$C_{23}H_{24}N_4O_3 = 404.477$

### Example 103

#### 1-[4-(N,N-dimethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

After adding 0.66 g (8.12 mmol) of dimethylamine hydrochloride and 1.86 ml (13.4 mmol) of triethylamine to a suspension of 1.5 g (4.06 mmol) of 1-(4-chloroacetyl-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 60 ml of ethanol, the reaction mixture was refluxed for 8 hours, then evaporated. The residue was dissolved in 30 ml of dichloromethane, washed with 20 ml of 4 % NaOH solution, then 2x20 ml of distilled water, dried and evaporated under reduced pressure. After treating with water, the crystalline residue was filtered to give 1.27 g of raw product, m.p. 211-213 °C. After recrystallization from 10 ml of ethanol 1.1 g (71.4 %) of aimed product were obtained, m.p.: 213-215 °C.

$C_{21}H_{22}N_4O_6 = 378.439$

### Example 104

#### 1-(4-Methylcarbamoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine

0.8 ml (13.4 mmol) of methyl isocyanate was added to a solution containing 1.0 g (3.41 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 8 ml of dimethylformamide (DMF), then the reaction mixture was stirred at 25 °C for 24 hours. After diluting with 80 ml of water, filtering at 5 °C and drying at 60 to 100 °C, 1.06 g of raw product, m.p.: 204-207 °C (sintering from 160 °C) were obtained which, when recrystallized from 5 ml of ethanol, gave 0.85 g (71.4 %) of the aimed product, m.p.: 223-224 °C (decomp.).

$C_{19}H_{18}N_4O_3 = 350.385$

### Example 105

#### 1-(4-Acetylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 42. The raw product was recrystallized from ethyl acetate to give 71.4 % of the aimed product, m.p.: 150-152 °C.

$C_{21}H_{22}N_4O_4 = 394.439$

### Example 106

#### 1-(4-Chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2, m.p.: 139-140 °C.

$C_{21}H_{20}ClN_3O_4 = 413.972$

### Example 107

#### 1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from the product of the preceding Example by using the process described in Example 103, m.p.: 206-208 °C.

$C_{23}H_{26}N_4O_4 = 422.493$

**Example 108**

**1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and diethylamine by using the process described in Example 102, m.p.: 175-176 °C.

$C_{25}H_{30}N_4O_4 = 450.547$

**Example 109**

**1-[4-(1-Pyrrolidinoacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrogen fumarate**

It was prepared from 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 2 and isolated in the form of hydrogen fumarate, m.p.: 181-183 °C (decomp.).

$[C_{25}H_{29}N_4O_4] \cdot C_4H_3O_4 = 564.607$

**Example 110**

**1-(4-Acetylaminophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from the compound of general formula (III), wherein  $R^4 = COCH_3$ , by using the process of Example 2 and chloroacetic acid instead of formic acid, m.p. 138-140 °C.

$C_{21}H_{20}ClN_3O_4 = 413.972$

**Example 111**

**1-[4-(N,N-diethylglycylamino)phenyl]-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine**

It was prepared from 1-(4-chloroacetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine by using the process of Example 102, except that diethylamine was used instead of pyrrolidine, m.p.: 157-158 °C.

$C_{23}H_{26}N_4O_3 = 406.493$

**Example 112**

**1-(4-Acetylaminophenyl)-3-cyclopropanecarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

It was prepared from 1-(4-aminophenyl)-3-cyclopropane-carbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 42, m.p.: 242-243 °C.

$C_{23}H_{23}N_3O_4 = 405.461$

**Example 113**

**N<sup>1</sup>-[4-(3-Methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)phenyl]-N<sup>3</sup>-methylurea**

After adding 0.5 ml (8.5 mmol) of methyl isocyanate to 0.6 g (1.7 mmol) of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) dissolved in 45 ml of anhydrous dichloromethane, the reaction mixture was stirred at 25 °C for 6 days. Then the crystalline precipitate was filtered, washed with 3x2 ml of dichloromethane and dried at 60 to 80 °C to obtain 0.55 g (79.7 %) of the pure aimed product, m.p.: 181-183 °C.

$C_{21}H_{23}N_5O_4 = 409.455$

## Example 114

## 1-(4-Aminophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-(4-nitrophenyl)-3-n-butylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine, m.p.: 173-175 °C.

$C_{22}H_{26}N_4O_3 = 394.482$

The starting substance was prepared as described for the starting substance of Example 98, except that n-butyl isocyanate was used instead of methyl isocyanate and the reaction mixture was stirred for 5 days at 25 °C, m.p. 176-178 °C.

$C_{22}H_{24}N_4O_5 = 424.466$

## Example 115

## 1-(4-Glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

It was prepared from 1-[4-(N-phthaloylglycylamino)-phenyl]-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine by using the process of Example 66 as modified in Example 82, m.p.: 163-165 °C.

$C_{21}H_{23}N_5O_4 = 409.455$

The starting substance was prepared from 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 98) according to Example 79, m.p. 270-271 °C (decomp.).

$C_{29}H_{25}N_5O_6 = 539.559$

## Example 116

## 1-(4-Aminophenyl)-3-(N-methylglycyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.03 g (15.3 mmol) of methylamine hydrochloride and 2.64 ml (18.3 mmol) of triethylamine were added to a suspension containing 1.23 g (3.06 mmol) of 1-(4-nitrophenyl)-3-chloroacetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine in 140 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was dissolved in 30 ml of chloroform, washed with 20 ml of 4% NaOH solution, then 2x20 ml of water, dried and evaporated under reduced pressure. The residue was reduced according to the process of Example 16 and the product obtained was purified by column chromatography (adsorbent: Kieselgel 60, eluent: methanol - benzene 4:1). The crude product obtained was triturated with 5 ml of ethyl acetate at 25 °C to obtain 0.60 g (53.6 %) of the aimed product, m.p. 198-200 °C (weak decomp.).

$C_{20}H_{22}N_4O_3 = 366.428$

The starting compound was obtained from 1-(4-nitrophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 26) and chloroacetic acid by using the process of Example 33, m.p. 189-191 °C (decomp.).

$C_{19}H_{16}ClN_3O_5 = 401.818$

## Example 117

## 1-[4-(N-methylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.31 g (19.5 mmol) of methylamine hydrochloride and 3.24 ml (23.3 mmol) of triethylamine were added to a suspension containing 1.61 g (3.89 mmol) of 1-(4-chloroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see Example 106) in 100 ml of ethanol and the reaction mixture was refluxed for 10 hours, then evaporated under reduced pressure. The residue was purified by column chromatography (adsorbent: Kieselgel 60, eluent: chloroform - methanol 9:1). The crude product was triturated with 3 ml of 50 % ethanol at 25 °C to give 0.61 g (38.6 %) of the aimed product, m.p.: 220-222 °C (weak decomp.).

$C_{22}H_{24}N_4O_4 = 408.466$

## Example 118

## Preparation of pharmaceutical compositions

Tablets or divided tablets containing 25 mg of 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Examples 15 or 16) or 25 mg of 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-

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7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 42) or 25 mg of 1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 98) each as active ingredient were prepared by usual methods.

### a) Composition of one tablet:

Active ingredient	25 mg
Potato starch	43 mg
Lactose	160 mg
Polyvinylpyrrolidone	6 mg
Magnesium stearate	1 mg
Talc	30 mg

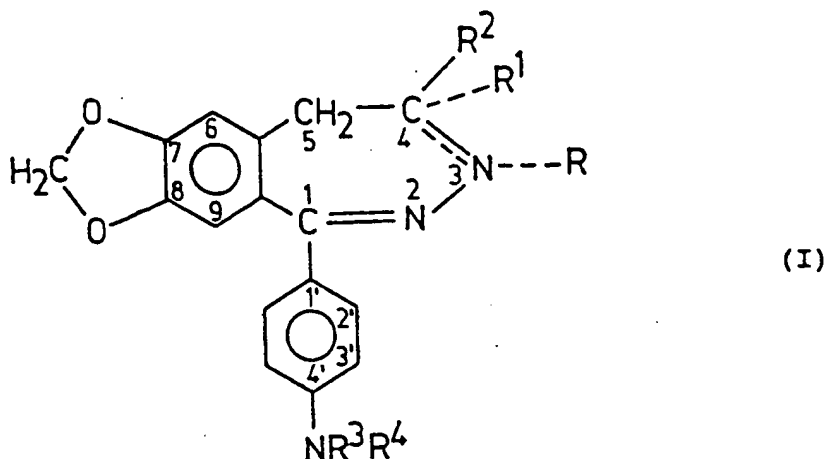
### b) Another preferred composition of one tablet:

Active ingredient	25 mg
Lactose	130 mg
Maize starch	25 mg
Microcrystalline cellulose	10 mg
Gelatine	4 mg
Talc	2 mg
Stearin	1 mg
Magnesium stearate	1 mg

## Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

### 1. N-Acyl-2,3-benzodiazepine derivatives of the general formula (I)



wherein

R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or

R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;

R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen, and their stereoisomers as well as acid-addition salts (where possible) of these compounds.

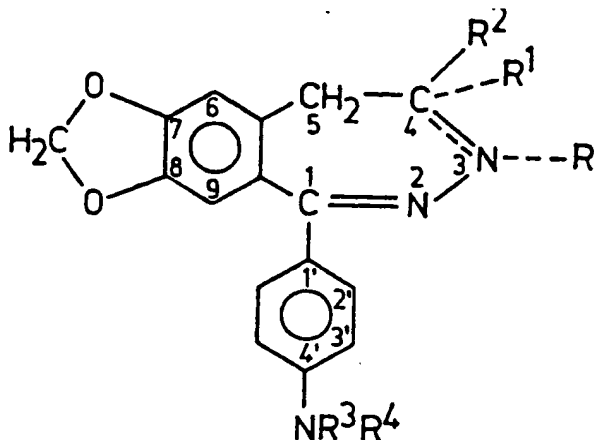
## 2. A compound selected from the group consisting of

- 1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrochloride,
- N<sup>1</sup>-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine-1-yl)-phenyl]-N<sup>3</sup>-methylurea,
- 1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,
- 1-[4-(1-pyrrolidinoacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine]

azepine and hydrogen fumarate thereof and

1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

3. A pharmaceutical composition, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.
4. A process for the preparation of the novel N-acyl-2,3-benzodiazepine derivatives of the general formula (I),



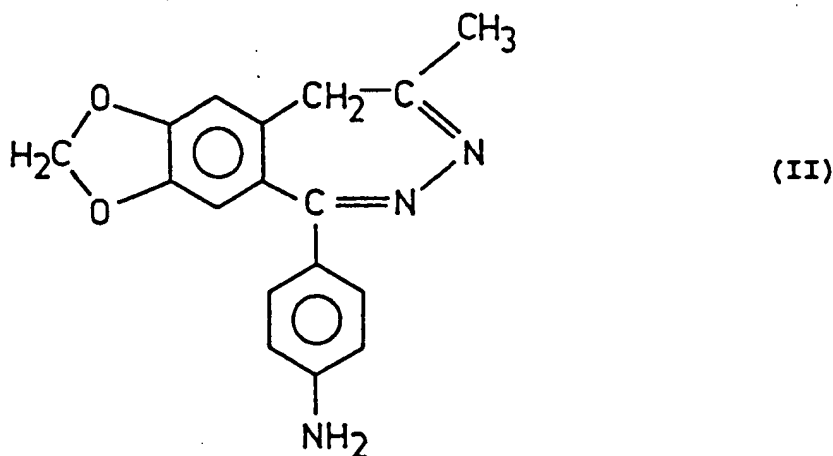
(I)

wherein

- R stands for a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;
- R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or
- R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;
- R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;
- R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

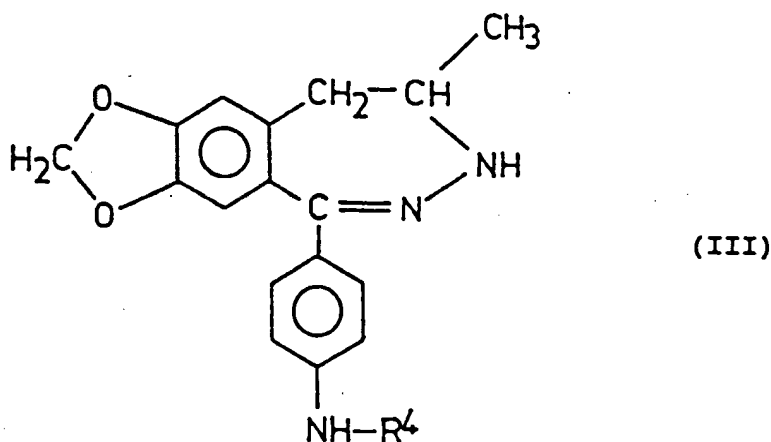
the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen, and their stereoisomers as well as acid addition salts, which comprises

a) acylating a compound of formula (II)



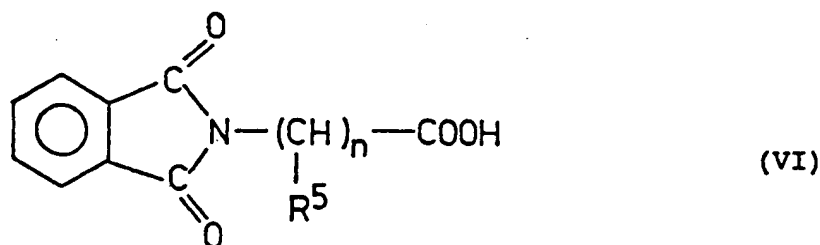
with a C<sub>1-6</sub> aliphatic carboxylic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

b) acylating a compound of the general formula (III),



wherein R<sup>4</sup> is as defined above, with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined above, R means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



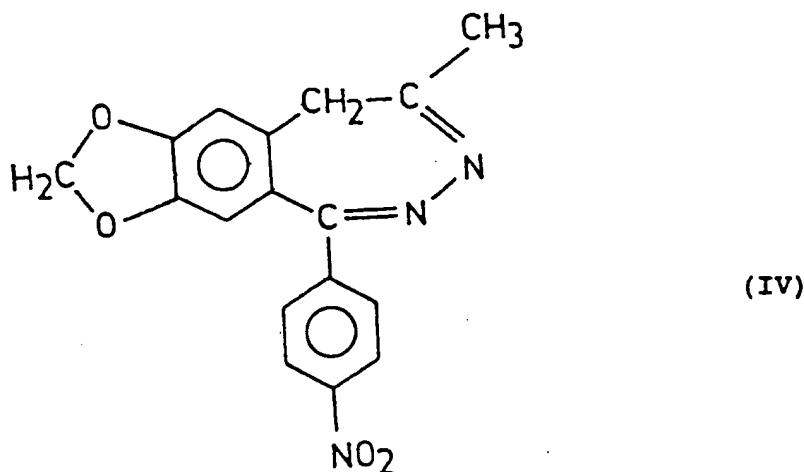
15 wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group, both  $R$  and  $R^1$  are absent, and a double bond is present between the N(3) and C(4) atoms; or

20 d) acylating a compound of the general formula (III), wherein  $R^4$  is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and  $n$  is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and  $n$  is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen,  $R$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

25 e) reacting a compound of the formula (II) with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  represents a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group,  $R$  and  $R^1$  are absent and a double bond is present between the N(3) and C(4) atoms; or

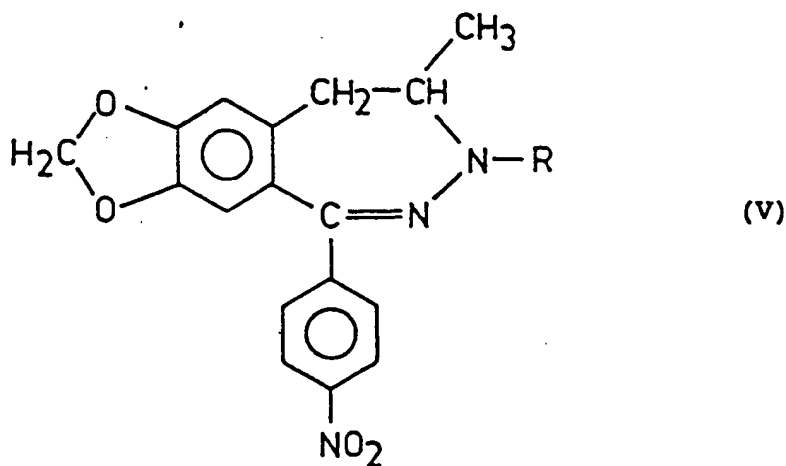
30 f) reacting a compound of the general formula (III), wherein  $R^4$  is defined as above, with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen,  $R$  stands for a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

35 g) selectively reducing a nitro compound of the formula (IV)



55 to a novel compound of the general formula (V)





wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein R<sup>4</sup> stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> represent hydrogen, R<sup>2</sup>, R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R and R<sup>4</sup> represent a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-5</sub> alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen; R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R represents a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen, R<sup>4</sup> represents a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

5. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.
6. A process as claimed in claim 4, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the pres-

ence of an acid-binding agent at a temperature between 0 °C and 150 °C.

7. A process as claimed in claim 6, which comprises carrying out the reaction in chloroform or dichloromethane.

8. A process as claimed in claim 4, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.

9. A process as claimed in claim 4, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C<sub>1-4</sub> aliphatic alcohol solution.

10. A process as claimed in claim 4, process g) or claim 6, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.

11. A process for the preparation of the pharmaceutical composition according to claim 3, which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

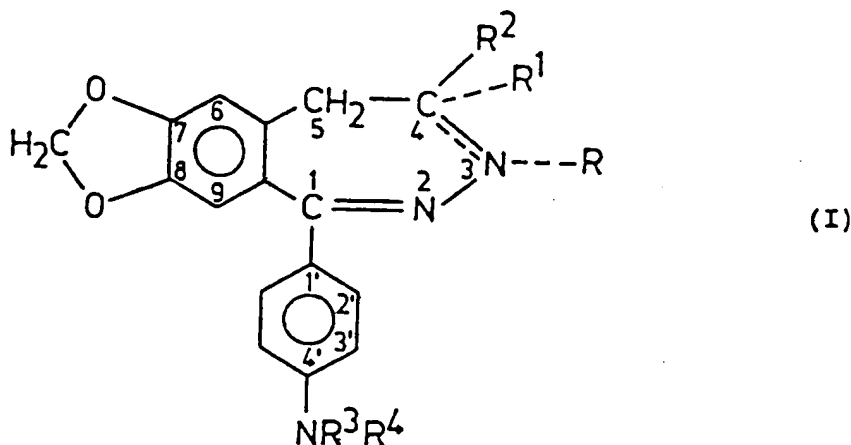
12. The use of the compounds prepared according to claims 1 to 8 for preparing medicaments, particularly such blocking one or more excitatory amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or such for treating epilepsy in mammals, or such for treating spasms of the skeletal musculature in mammals by muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals.

13. N-Acyl-2,3-benzodiazepine derivatives of the general formula V, as given in claim 4, wherein

R means hydrogen or a C<sub>1-6</sub> aliphatic acyl group; optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group.

Claims for the following Contracting States : GR, ES

1. A process for the preparation of N-acyl-2,3-benzodiazepine derivatives of the general formula (I),



wherein

R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; or R is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>1</sup> means hydrogen; or R<sup>1</sup> is absent when a double bond exists between the N(3) and C(4) atoms;

R<sup>2</sup> means a C<sub>1-3</sub> alkyl group; or

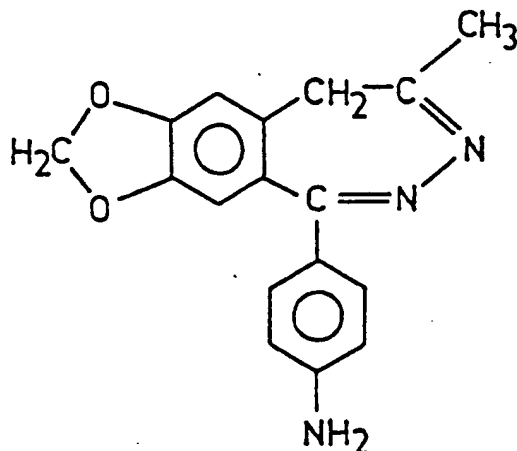
R<sup>1</sup> and R<sup>2</sup> together stand for a methylene group and no double bond is present between the N(3) and C(4) atoms;

R<sup>3</sup> means hydrogen or a C<sub>1-4</sub> aliphatic acyl group;

R<sup>4</sup> represents hydrogen; a C<sub>1-6</sub> aliphatic acyl group optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group or by one or more halogen(s); as well as a benzoyl, palmitoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group; and

the dotted lines represent valence bonds optionally being present, with the proviso that no double bond exists between the N(3) and C(4) atoms when both R<sup>3</sup> and R<sup>4</sup> stand for hydrogen, and their stereoisomers as well as acid addition salts, which comprises

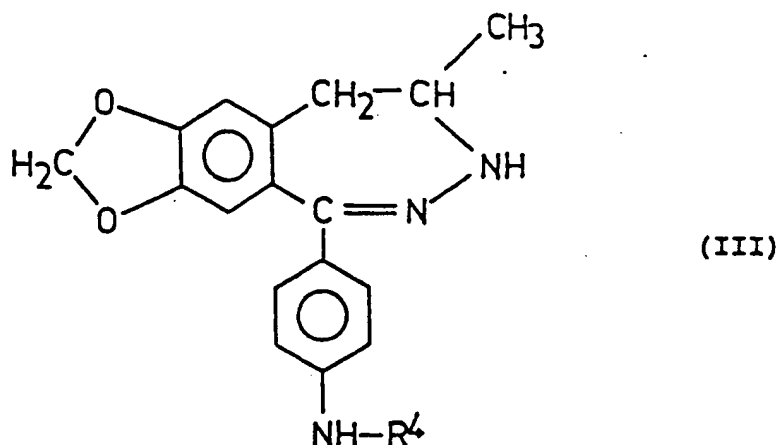
a) acylating a compound of formula (II)



(II)

with a C<sub>1-6</sub> aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group substituted by a halogen, with a C<sub>1-4</sub> alkylamine, di(C<sub>1-4</sub> alkyl)amine or pyrrolidine, to obtain compounds of the general formula (I), wherein R<sup>2</sup>, R<sup>3</sup> and the dotted lines are as defined above, R<sup>4</sup> means a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R<sup>1</sup> are absent and a double bond is present between the N(3) and C(4) atoms;

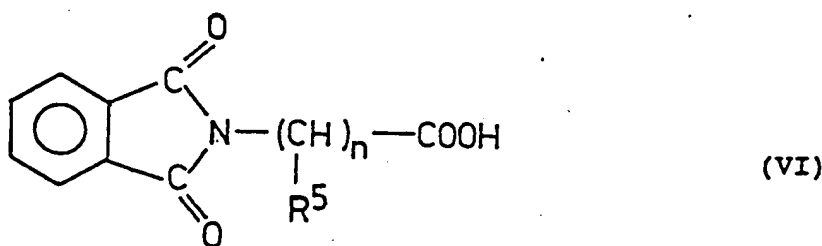
b) acylating a compound of the general formula (III),



wherein  $R^4$  is as defined above, with a  $C_{1-6}$  aliphatic carboxylic acid, optionally substituted by a methoxy, cyano, carboxy or phenyl group or by one or more halogen(s); or with benzoic or cyclopropanecarboxylic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of general formula (I) thus obtained, wherein  $R^4$  means a  $C_{1-6}$  aliphatic acyl group substituted by a halogen, with a  $C_{1-4}$  alkylamine, di( $C_{1-4}$  alkyl)amine or pyrrolidine,

to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and the dotted lines are as defined above, R means a  $C_{1-6}$  aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxy, phenyl,  $C_{1-4}$  alkylamino, di( $C_{1-4}$  alkyl)amino or pyrrolidino group, or one or more halogen(s); or a benzoyl or a cyclopropanecarbonyl group; and no double bond exists between the N(3) and C(4) atoms; or

c) acylating a compound of formula (II) with an N-phthaloylamino acid of the general formula (VI),



wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and n is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and n is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group, both R and  $R^1$  are absent, and a double bond is present between the N(3) and C(4) atoms; or

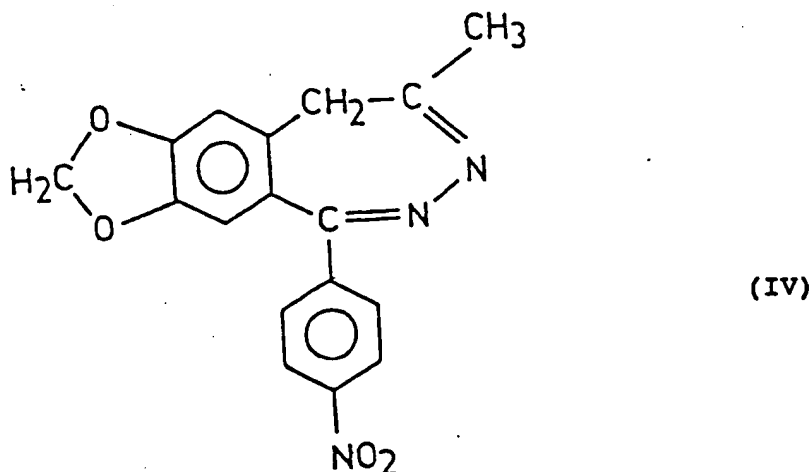
d) acylating a compound of the general formula (III), wherein  $R^4$  is as defined above, with an N-phthaloylamino acid of the general formula (VI), wherein  $R^5$  stands for hydrogen or a  $C_{1-4}$  alkyl group and n is 1 in case of  $\alpha$ -amino acids, whereas  $R^5$  means hydrogen and n is an integer of 2 to 5 in case of  $\beta$ - $\epsilon$  amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen, R stands for a  $C_{1-6}$  aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms; or

e) reacting a compound of the formula (II) with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^2$  and the dotted lines are as defined above,  $R^3$  means hydrogen,  $R^4$  represents a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group, R and  $R^1$  are absent and a double bond is present between the N(3) and C(4) atoms; or

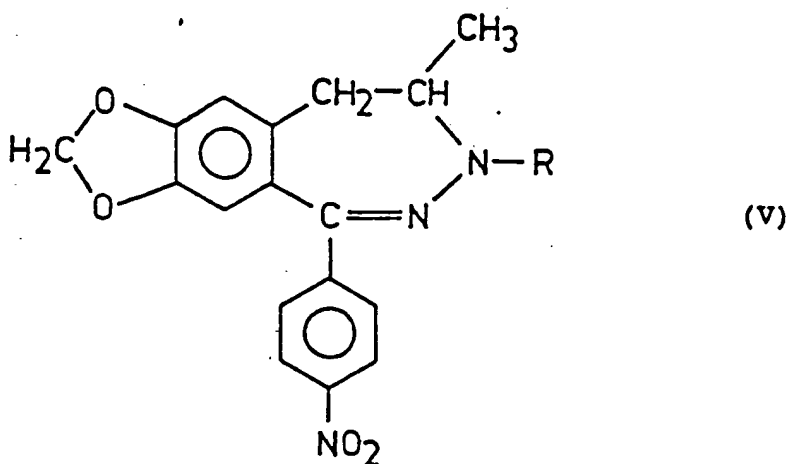
f) reacting a compound of the general formula (III), wherein  $R^4$  is defined as above, with a  $C_{1-5}$  alkyl isocyanate or phenyl isocyanate, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$  and the dotted lines are

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as defined above,  $R^3$  means hydrogen,  $R^4$  is as defined above except hydrogen, R stands for a  $C_{1-5}$  alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or  
g) selectively reducing a nitro compound of the formula (IV)



to a novel compound of the general formula (V)



wherein R means hydrogen, then either acylating the compound of general formula (V) thus obtained by using any of the above processes b), d) or f) and reducing the nitro group of the thus-obtained new compound of general formula (V), wherein R is as defined above, to an amino group, or first reducing the nitro group and then acylating the compound of general formula (III) thus obtained, wherein  $R^4$  stands for hydrogen, by using any of the above processes b), d) or f), to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^3$  and  $R^4$  represent hydrogen,  $R^2$ , R and the dotted lines are as defined above and no double bond is present between the N(3) and C(4) atoms; or

h) acylating a new compound of the general formula (I), wherein R,  $R^1$ ,  $R^2$  and the dotted lines are as defined above,  $R^3$  and  $R^4$  mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a  $C_{1-6}$  aliphatic carboxylic acid, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or with benzoic acid; or with a reactive derivative thereof, to obtain compounds of the general formula (I), wherein  $R^1$ ,  $R^2$ ,  $R^3$  and the dotted lines are as defined above, R and  $R^4$  represent a  $C_{1-6}$  aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; and no double bond is present between the N(3) and C(4) atoms; or

i) reacting a new compound of the general formula (I), wherein R,  $R^1$ ,  $R^2$  and the dotted lines are as defined

above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with a C<sub>1-5</sub> alkyl isocyanat , to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R stands for a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group, or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen; R<sup>4</sup> represents a C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group and no double bond is present between the N(3) and C(4) atoms; or

j) acylating a new compound of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R<sup>3</sup> and R<sup>4</sup> mean hydrogen and no double bond is present between the N(3) and C(4) atoms, with an N-phthaloylamino acid of the general formula (VI), wherein R<sup>5</sup> stands for hydrogen or a C<sub>1-4</sub> alkyl group and n is 1 in case of α-amino acids, whereas R<sup>5</sup> means hydrogen and n is an integer of 2 to 5 in case of β-ε amino acids, and, if desired, removing the phthaloyl group, to obtain compounds of the general formula (I), wherein R<sup>1</sup>, R<sup>2</sup> and the dotted lines are as defined above, R represents a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano or carboxy group or by one or more halogen(s); or a benzoyl group; R<sup>3</sup> stands for hydrogen, R<sup>4</sup> represents a C<sub>1-6</sub> aliphatic acyl group substituted by an amino or phthalimido group and no double bond is present between the N(3) and C(4) atoms,

and, if desired, transforming a base of the general formula (I), obtained by any of the above processes a) to j), to an acid-addition salt.

2. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in a suitable solvent, preferably dichloromethane, with a carboxylic acid in the presence of dicyclohexylcarbodiimide at a temperature between 10 °C and 30 °C.
3. A process as claimed in claim 1, process a) or b), which comprises carrying out the acylation in the presence or absence of a solvent by using a carboxylic acid anhydride, mixed anhydride or acyl chloride, optionally in the presence of an acid-binding agent at a temperature between 0 °C and 150 °C.
4. A process as claimed in claim 3, which comprises carrying out the reaction in chloroform or dichloromethane.
5. A process as claimed in claim 1, process e) or f), which comprises carrying out the additive acylation by using a suitable alkyl or phenyl isocyanate in dimethylformamide, benzene or dichloromethane at a temperature between 15 °C and 100 °C.
6. A process as claimed in claim 1, process g), which comprises carrying out the selective reduction of the nitro compound of formula (IV) using sodium borohydride in a C<sub>1-4</sub> aliphatic alcohol solution.
7. A process as claimed in claim 1, process g) or claim 3, which comprises reducing the nitro group of a compound of the general formula (V) in a methanolic medium by using hydrazine or hydrazine hydrate in the presence of Raney nickel or palladium as catalyst at a temperature between 10 °C and 65 °C.
8. A process according to anyone of claims 1 to 7, characterized in that a compound selected from the group consisting of

1-(4-aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-propionylaminophenyl)-3-formyl-4-methyl-7,8-methylene-dioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-trifluoroacetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-(4-glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine hydrochloride,  
 N<sup>1</sup>-[4-(3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine-1-yl)-phenyl]-N<sup>3</sup>-methylurea,  
 1-[4-(N,N-dimethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,  
 1-[4-(N,N-diethylglycylamino)phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine,

1-[4-(1-pyrrolidinoacetyl)amino]phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine and hydrogen fumarate thereof and

1-(4-glycylaminophenyl)-3-methylcarbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine is prepared.

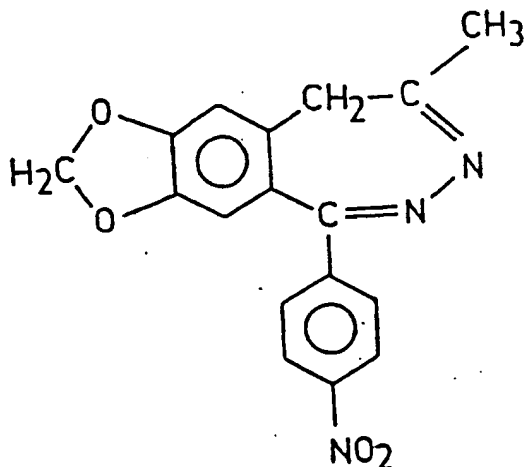
9. A process for the preparation of a pharmaceutical composition which comprises as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry, characterized by admixing as active ingredient a novel N-acyl-2,3-benzodiazepine derivative of the general formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and the dotted lines are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, prepared by using any of process variants a) to j) as claimed in claim 1, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

10. A process according to claim 9, characterized in that compositions for blocking one or more excitatory amino acid receptors in mammals in need of decreased excitatory amino acid neurotransmission, or for treating epilepsy in mammals, or for treating spasms of the skeletal musculature in mammals by muscle-relaxing or for treating cerebral ischaemia (stroke) in mammals are prepared.

11. A process for preparing N-acyl-2,3-benzodiazepine derivatives of the general formula V, as given in claim 1, wherein

R means hydrogen or a C<sub>1-6</sub> aliphatic acyl group, optionally substituted by a methoxy, cyano, carboxyl, amino, C<sub>1-4</sub> alkylamino, di(C<sub>1-4</sub> alkyl)amino, pyrrolidino, phthalimido or phenyl group, or by one or more halogen(s); or R is a benzoyl, cyclopropanecarbonyl, C<sub>1-5</sub> alkylcarbamoyl or phenylcarbamoyl group,

characterized by selectively reducing a nitro compound of the formula selectively reducing a nitro compound of the formula (IV)

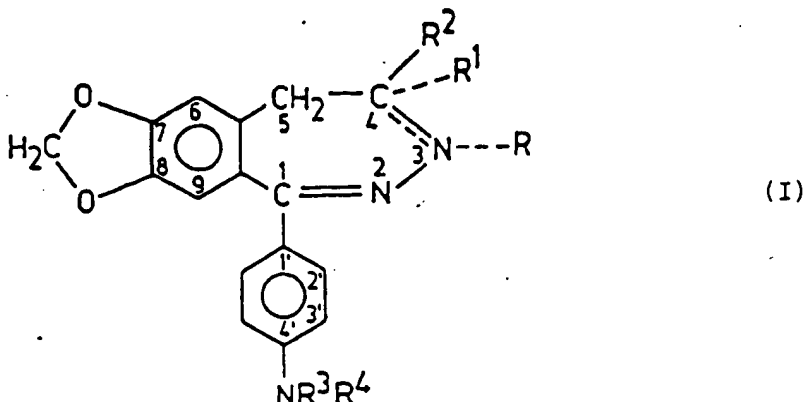


(IV).

# Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. N-Acyl-2,3-benzodiazepin-Derivate der allgemeinen Formel (I),



worin

- R eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, di(C<sub>1-4</sub> Alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; oder
- R eine Benzoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; oder
- R abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;
- R<sup>1</sup> ein Wasserstoffatom bedeutet; oder
- R<sup>1</sup> abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;
- R<sup>2</sup> eine C<sub>1-3</sub> Alkylgruppe bedeutet; oder
- R<sup>1</sup> und R<sup>2</sup> zusammen für eine Methylengruppe stehen und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist;
- R<sup>3</sup> Wasserstoffatom oder eine C<sub>1-4</sub> aliphatische Acylgruppe bedeutet;
- R<sup>4</sup> ein Wasserstoffatom; eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; sowie eine Benzoyl-, Palmitoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; und

die gestrichelten Linien gegebenenfalls anwesende Valenzbindungen bedeuten, mit der Beschränkung, dass zwischen den N(3) und C(4) Atomen keine Doppelbindung existiert, wenn sowohl R<sub>3</sub> als auch R<sub>4</sub> Wasserstoff bedeuten, und ihre Stereoisomere sowie die Säureadditionssalze (wenn möglich) dieser Verbindungen.

2. Eine Verbindung gewählt aus der Gruppe, die aus folgenden Verbindungen besteht:

- 1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Propionylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Propionylaminophenyl)-3-formyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Trifluoracetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
 1-(4-Glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin hydrochlorid,  
 N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-methylcarbamid,  
 1-[4-(N,N-Dimethylglycylamino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,



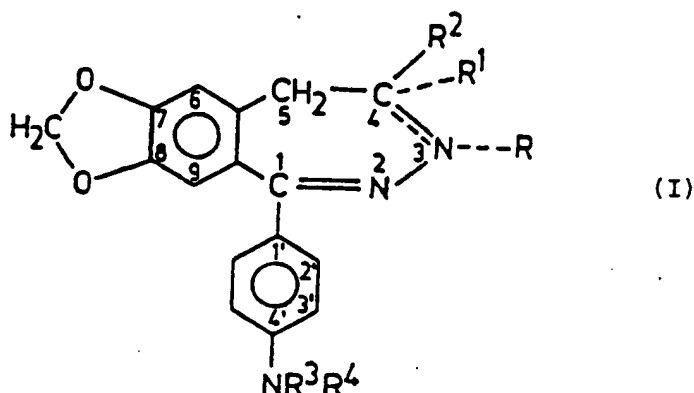
1-[4-(N,N-diethylglycylamino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,

1-[4-(1-Pyrrolidinoacetyl-amino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin und sein Wasserstoff-fumarat und

1-(4-Glycylaminophenyl)-3-methyl-carbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin.

3. Eine pharmazeutische Komposition, die als aktive Komponente ein neues N-Acyl-2,3-benzodiazepin-Derivat der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie im Patentanspruch 1 definiert sind, oder ein pharmazeutisch annehmbares Säureadditionssalz davon, gemischt mit in der pharmazeutischen Industrie allgemein verwendeten Trägerstoffen und/oder Zusatzstoffen, enthält.

4. Verfahren zur Herstellung der neuen N-Acyl-2,3-benzodiazepin-Derivate der allgemeinen Formel (I),



worin

R eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; oder R eine Benzoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; oder R abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;

R<sup>1</sup> Wasserstoffatom bedeutet; oder R<sup>1</sup> abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;

R<sup>2</sup> eine C<sub>1-3</sub> Alkylgruppe bedeutet; oder

R<sup>1</sup> und R<sup>2</sup> zusammen für eine Methylengruppe stehen und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist;

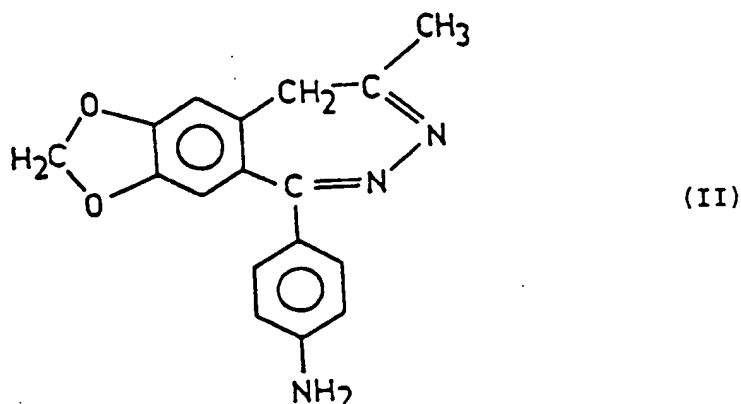
R<sup>3</sup> Wasserstoffatom oder eine C<sub>1-4</sub> aliphatische Acylgruppe bedeutet;

R<sup>4</sup> ein Wasserstoffatom; eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4a</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; sowie R<sup>4</sup> eine Benzoyl-, Palmitoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; und

die gestrichelten Linien gegebenenfalls anwesende Valenzbindungen bedeuten, mit der Beschränkung, dass zwischen den N(3) und C(4) Atomen keine Doppelbindung existiert, wenn sowohl R<sub>3</sub> als auch R<sub>4</sub> Wasserstoff bedeuten,

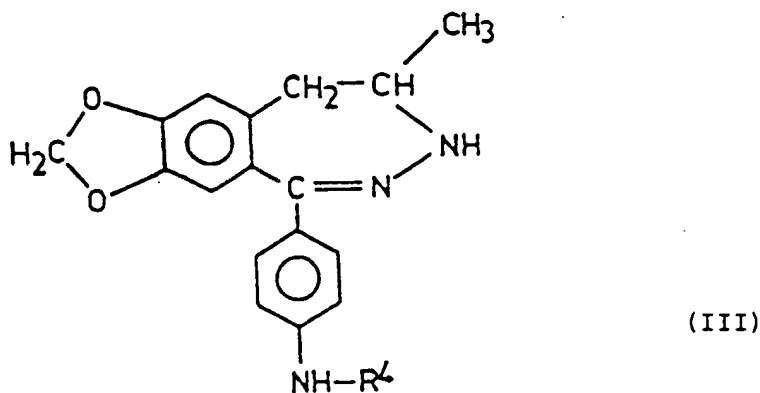
und ihre Stereoisomere sowie die Säureadditionssalze, dadurch gekennzeichnet, dass

a) eine Verbindung der Formel (II)



20 mit einer C<sub>1-6</sub> aliphatischen Carboxylsäure, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure, Cyclopropancarboxylsäure oder Palmitinsäure oder mit einem reaktionsfähigen Derivat davon acyliert wird; und gewünschtenfalls eine derart erhaltene neue Verbindung der allgemeinen Formel (I), worin R<sup>4</sup> eine mit einem Halogenatom substituierte C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, mit einem C<sub>1-4</sub> Alkylamin, Di(C<sub>1-4</sub> alkyl)-amin oder Pyrrolidin umgesetzt wird, um Verbindungen der Formel (I) zu erhalten, worin R<sup>2</sup>, R<sup>3</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>4</sup> eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Phenyl-, C<sub>1-4</sub> Alkyl-amino, DiC<sub>1-4</sub> alkyl)-amino- oder Pyrrolidinogruppe, oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder R<sup>4</sup> eine Benzoyl-, Cyclopropancarboxyl- oder Palmitoylgruppe bedeutet; R und R<sup>1</sup> abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist;

30 b) eine Verbindung der allgemeinen Formel (III),

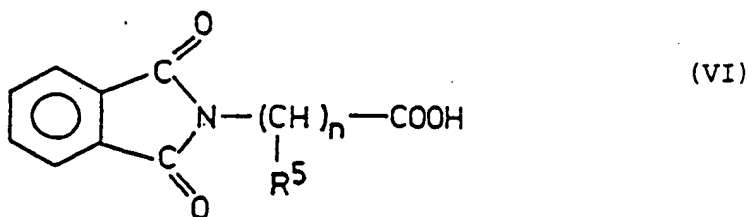


50 worin

R<sup>4</sup> wie oben definiert ist, mit einer C<sub>1-6</sub> aliphatischen Carboxylsäure, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure oder Cyclopropancarbonsäure oder mit einem reaktiven Derivat davon acyliert wird; und gewünschtenfalls eine derart erhaltene neue Verbindung der allgemeinen Formel (I), worin R<sup>4</sup> eine durch ein Halogenatom substituierte C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, mit einem C<sub>1-4</sub> Alkylamin, Di(C<sub>1-4</sub> alkyl)-amin oder Pyrrolidin umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie oben definiert sind, R eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Phenyl-, C<sub>1-4</sub> Alkylamino, Di(C<sub>1-4</sub> alkyl)-amino- oder Pyrrolidinogruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder eine Benzoyl- oder Cyclopropancarboxylgruppe bedeutet; und zwischen den N(3) und C(4) Atomen keine Doppelbindung existiert;

stiert; oder

c) eine Verbindung der Formel (II) mit einer N-Phthaloylaminosäure der allgemeinen Formel (VI),



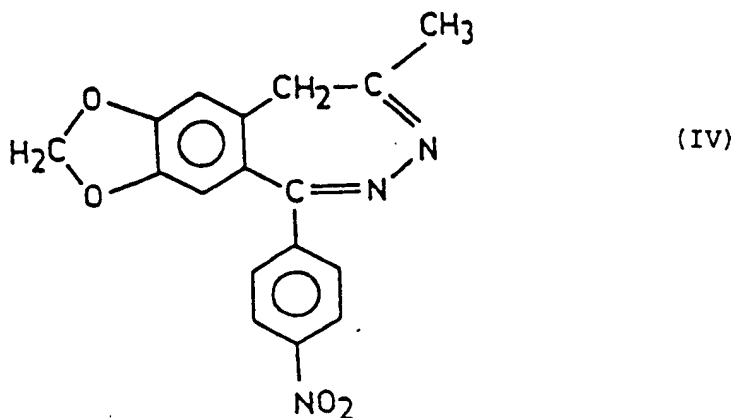
worin im Falle von  $\alpha$ -Aminosäuren  $R^5$  für Wasserstoffatom oder eine  $C_{1-4}$  Alkylgruppe steht und  $n$  1 ist, wogegen im Falle von  $\beta$ - $\epsilon$ -Aminosäuren  $R^5$  für Wasserstoffatom steht und  $n$  eine ganze Zahl von 2 bis 5 ist, acyliert wird, und gewünschtenfalls die Phthaloylgruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^2$  und die gestrichelten Linien die oben definierten Bedeutungen haben,  $R^3$  Wasserstoff bedeutet,  $R^4$  für eine durch eine Amino- oder Phthalimidogruppe substituierte  $C_{1-6}$  aliphatische Acylgruppe steht, sowohl  $R$  als auch  $R^1$  abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist; oder

d) eine Verbindung der allgemeinen Formel (III), worin  $R^4$  wie oben definiert ist, mit einer N-Phthaloylaminosäure der allgemeinen Formel (VI) acyliert wird, worin im Falle von  $\alpha$ -Aminosäuren  $R^5$  für Wasserstoffatom oder eine  $C_{1-4}$  Alkylgruppe steht und  $n$  1 ist, wogegen im Falle von  $\beta$ - $\epsilon$ -Aminosäuren  $R^5$  Wasserstoff bedeutet und  $n$  eine ganze Zahl von 2 bis 5 ist, und gewünschtenfalls die Phthaloylgruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^1$ ,  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  mit der Ausnahme von Wasserstoff wie oben definiert ist,  $R$  für eine durch eine Amino- oder Phthalimidogruppe substituierte  $C_{1-6}$  aliphatische Acylgruppe steht, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

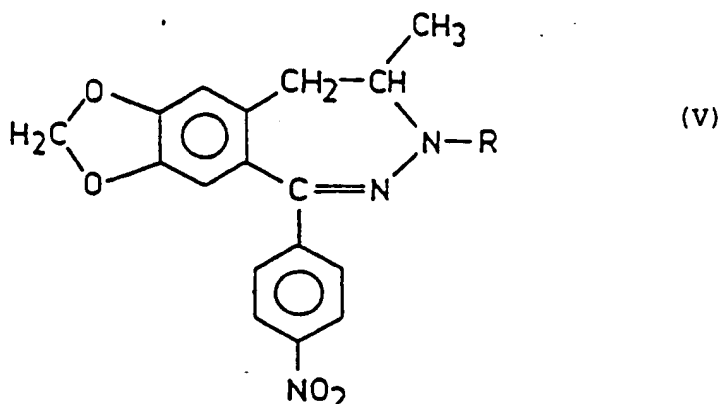
e) eine Verbindung der Formel (II) mit einem  $C_{1-5}$  Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  eine  $C_{1-5}$  Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet,  $R$  und  $R^1$  abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist; oder

f) eine Verbindung der allgemeinen Formel (III), worin  $R^4$  wie oben definiert ist, mit einem  $C_{1-5}$  Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^1$  und  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  mit der Ausnahme von Wasserstoff wie oben definiert ist,  $R$  eine  $C_{1-5}$  Alkylcarbamoyl- oder Phenylcarbamoylgruppe steht, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

g) eine Verbindung der allgemeinen Formel (IV)



selektiv zu einer neuen Verbindung der allgemeinen Formel (V)



reduziert wird, worin R Wasserstoff bedeutet, dann entweder die derart erhaltene Verbindung der allgemeinen Formel (V) durch Verwendung einer der obigen Verfahren b), d) oder f) acyliert und die Nitrogruppe der derart erhaltenen neuen Verbindung der allgemeinen Formel (V), worin R wie oben definiert ist, zu einer Aminogruppe reduziert wird, oder zuerst die Nitrogruppe reduziert und dann die derart erhaltene Verbindung der allgemeinen Formel (III), worin R<sup>4</sup> für Wasserstoff steht, acyliert durch Verwendung einer der obigen Verfahren b), d) oder f), um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>3</sup>, und R<sup>4</sup> Wasserstoff bedeuten, R<sup>2</sup>, R und die gestrichelten Linien wie oben definiert sind, und zwischen den N(3) und C(4) Atome keine Doppelbindung anwesend ist; oder

h) eine neue Verbindung der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einer C<sub>1-6</sub> aliphatischen Carbonsäure, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure oder mit einem reaktionsfähigen Derivat davon acyliert wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> und die gestrichelten Linien wie oben definiert sind, R und R<sup>4</sup> eine C<sub>1-6</sub> aliphatische Acylgruppe bedeuten, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert sind; oder eine Benzoylgruppe bedeuten; und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

i) eine neue Verbindung der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einem C<sub>1-5</sub> Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R für eine C<sub>1-6</sub> aliphatische Acylgruppe steht, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder eine Benzoylgruppe steht; R<sup>3</sup> für Wasserstoff steht; R<sup>4</sup> eine C<sub>1-5</sub> Alkylcarbonyl- oder Phenylcarbonylgruppe bedeutet; und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

j) eine neue Verbindung der allgemeinen Formel (I), worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einer N-Phthaloylaminosäure der allgemeinen Formel (VI), worin im Falle von α-Aminosäuren R<sup>5</sup> für Wasserstoff oder eine C<sub>1-4</sub> Alkylgruppe steht und n 1 ist, wogegen im Falle von β-ε-Aminosäuren R<sup>5</sup> Wasserstoff bedeutet und n eine ganze Zahl vom 2 bis 5 ist, acyliert wird, und gegebenenfalls die Phthaloylgruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder R eine Benzoylgruppe bedeutet; R<sup>3</sup> für Wasserstoff steht, R<sup>4</sup> eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die durch eine Amino- oder Phthalimidogruppe substituiert ist, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist,

und gegebenenfalls eine Base der allgemeinen Formel (I), die durch eines der obigen Verfahren a) bis j) erhalten wurde, in ein Säureadditionssalz umgestaltet wird.

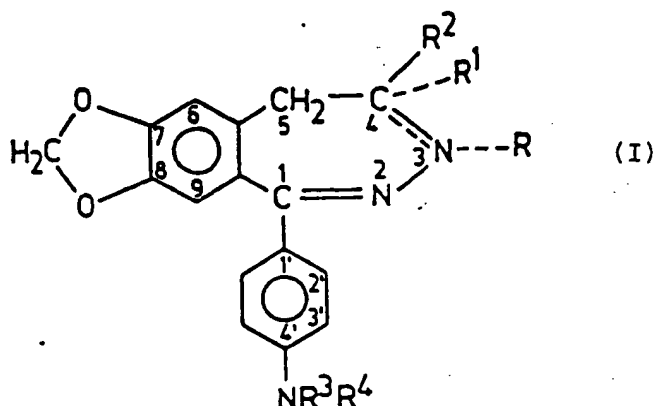
5. Verfahren nach Patentanspruch 4, Verfahren a) oder b), dadurch gekennzeichnet, dass die Acylierung in einem

entsprechenden Lösungsmittel, vorzugsweise Dichlormetan, mit einer Carbonsäure in der Anwesenheit von Dicyclohexylcarbodiimid bei einer Temperatur zwischen 10 und 30 °C durchgeführt wird.

- 5 6. Verfahren nach Patentanspruch 4, Verfahren a) oder b), dadurch gekennzeichnet, dass die Acylierung in Gegenwart oder Abwesenheit eines Lösungsmittels, durch Verwendung eines Carbonsäureanhydrids, gemischten Anhydrids oder Acylchlorids, gegebenenfalls in Gegenwart eines Säurebindemittels, bei einer Temperatur zwischen 0 °C und 150 °C durchgeführt wird.
- 10 7. Verfahren nach Patentanspruch 6, dadurch gekennzeichnet, dass die Reaktion in Chloroform oder Dichlormethan durchgeführt wird.
- 15 8. Verfahren nach Patentanspruch 4, Verfahren e) oder f), dadurch gekennzeichnet, dass die additive Acylierung durch Verwendung eines entsprechenden Alkyl- oder Phenylisocyanates in Dimethylformamid, Benzol oder Dichlormethan bei einer Temperatur zwischen 15 °C und 100 °C durchgeführt wird.
- 20 9. Verfahren nach Patentanspruch 4, Verfahren g), dadurch gekennzeichnet, dass die selektive Reduktion der Nitroverbindung der Formel (IV) durch Verwendung von Natriumborhydrid in einer Lösung eines C<sub>1-5</sub> aliphatischen Alkohols durchgeführt wird.
- 25 10. Verfahren nach Patentanspruch 4, Verfahren g) oder Patentanspruch 6, dadurch gekennzeichnet, dass die Reduktion der Nitrogruppe einer Verbindung der allgemeinen Formel (V) in einem methanolischen Medium, durch Verwendung von Hydrazin oder Hydrazinhydrat, in Gegenwart von Raney-Nickel oder Palladium als Katalysator bei einer Temperatur zwischen 10 °C und 65 °C durchgeführt wird.
- 30 11. Verfahren für die Herstellung einer pharmazeutischen Komposition nach Patentanspruch 3, dadurch gekennzeichnet, dass als Wirkungsstoff ein neues N-Acyl-2,3-Benzodiazepin-Derivat der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie im Patentanspruch 1 definiert sind, oder ein pharmazeutisch annehmbares Säureadditionssalz davon mit in der pharmazeutischen Industrie üblich verwendeten Trägerstoffen und/oder Zusatzstoffen zu einer pharmazeutischen Komposition umgestaltet wird.
- 35 12. Verwendung der gemäß den Patentansprüchen 1 bis 8 hergestellten Verbindungen für Herstellung von Heilmitteln, besonders von solchen, die einen oder mehreren stimulierenden Aminosäure-Rezeptor in Säugetieren, die verminderte stimulierende Aminosäure-Neurotransmission brauchen, blockieren, oder von solchen, die für die Behandlung von Epilepsie in Säugetieren dienen, oder von solchen, die zur Behandlung von Spasmen der skeletalen Muskulatur in Säugetieren durch Muskelrelaxation oder für die Behandlung von Gehirnschämie (Stroke) in Säugetieren geeignet sind.
- 40 13. N-Acyl-2,3-benzodiazepin-Derivate der allgemeinen Formel (V) wie in Patentanspruch 4 gegeben, worin  
R Wasserstoff oder eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder R eine Benzoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl oder Phenylcarbamoylgruppe bedeutet.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung von N-Acyl-2,3-benzodiazepin-Derivaten der allgemeinen Formel (I),

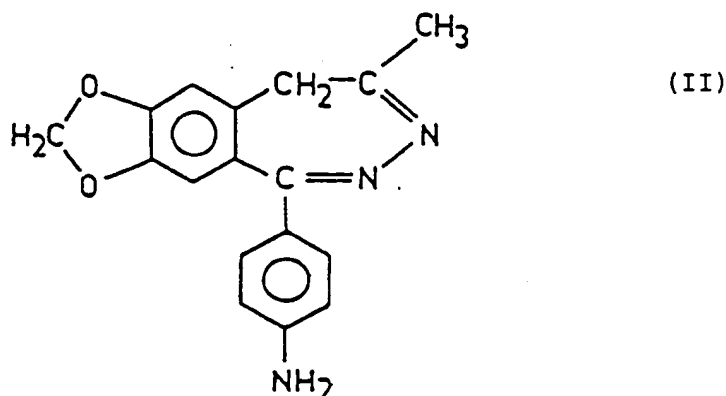


- R eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; oder R eine Benzoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; oder R abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;
- R<sup>1</sup> Wasserstoffatom bedeutet; oder R<sup>1</sup> abwesend ist, wenn zwischen den N(3) und C(4) Atomen eine Doppelbindung existiert;
- R<sup>2</sup> eine C<sub>1-3</sub> Alkylgruppe bedeutet; oder
- R<sup>1</sup> und R<sub>2</sub> zusammen für eine Methylengruppe stehen und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist;
- R<sup>3</sup> Wasserstoffatom oder eine C<sub>1-4</sub> aliphatische Acylgruppe bedeutet;
- R<sup>4</sup> ein Wasserstoffatom; eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino-, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist, bedeutet; sowie R<sup>4</sup> eine Benzoyl-, Palmitoyl-, Cyclopropancarbonyl-, C<sub>1-5</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet; und

die gestrichelten Linien gegebenenfalls anwesende Valenzbindungen bedeuten, mit der Beschränkung, dass zwischen den N(3) und C(4) Atomen keine Doppelbindung existiert, wenn sowohl R<sub>3</sub> als auch R<sub>4</sub> Wasserstoff bedeuten,

und ihre Stereoisomere sowie die Säureadditionssalze, dadurch gekennzeichnet, dass

a) eine Verbindung der Formel (II)

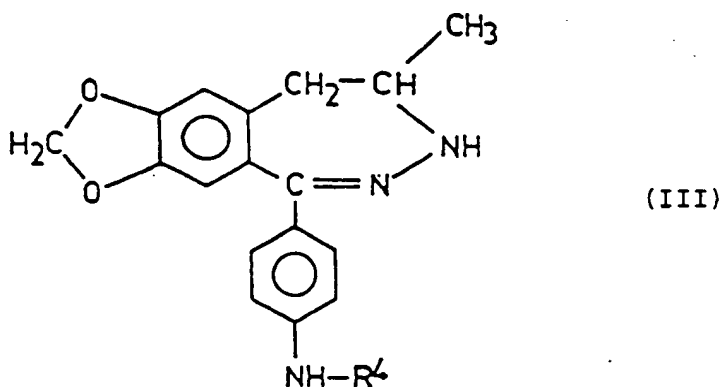


20 mit einer C<sub>1-6</sub> aliphatischen Carboxylsäure, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure, Cyclopropan-carboxylsäure oder Palmitinsäure oder mit einem reaktionsfähigen Derivat davon acyliert wird; und

25 gewünschtenfalls eine derart erhaltene neue Verbindung der allgemeinen Formel (I), worin R<sup>4</sup> eine mit einem Halogenatom substituierte C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, mit einem C<sub>1-4</sub> Alkylamin, Di(C<sub>1-4</sub> alkyl)-amin oder Pyrrolidin umgesetzt wird, um Verbindungen der Formel (I) zu erhalten, worin R<sup>2</sup>, R<sup>3</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>4</sup> eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Phenyl, C<sub>1-4</sub> Alkyl-amino, DiC<sub>1-4</sub> alkyl)-amino- oder Pyrrolidinogruppe, oder

30 durch ein oder mehrere Halogenatom(e) substituiert ist; oder R<sup>4</sup> eine Benzoyl-, Cyclopropan-carbonyl- oder Palmitoylgruppe bedeutet; R und R<sup>1</sup> abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist;

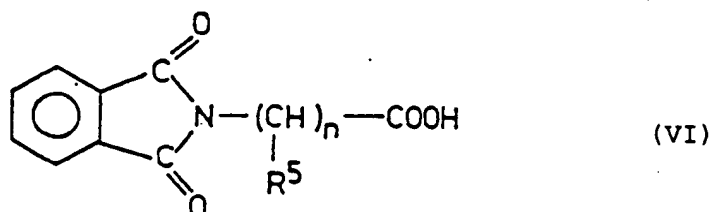
b) eine Verbindung der allgemeinen Formel (III),



worin

50 R<sup>4</sup> wie oben definiert ist, mit einer C<sub>1-6</sub> aliphatischen Carboxylsäure, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure oder Cyclopropan-carboxylsäure oder mit einem reaktiven Derivat davon acyliert wird; und gewünschtenfalls eine derart erhaltene neue Verbindung der allgemeinen Formel (I), worin R<sup>4</sup> eine durch ein Halogenatom substituierte C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, mit einem C<sub>1-4</sub> Alkylamin, Di(C<sub>1-4</sub> alkyl)-amin oder Pyrrolidin umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie oben definiert sind, R eine C<sub>1-6</sub> aliphatische Acylgruppe, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Phenyl, C<sub>1-4</sub> Alkyl-amino, Di(C<sub>1-4</sub> alkyl)-amino- oder Pyrrolidinogruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder eine Benzoyl- oder Cyclopropan-carbonylgruppe bedeutet; und zwischen den N(3) und C(4) Atomen keine Doppelbindung existiert; oder

c) eine Verbindung der Formel (II) mit einer N-Phthaloylaminosäure der allgemeinen Formel (VI),



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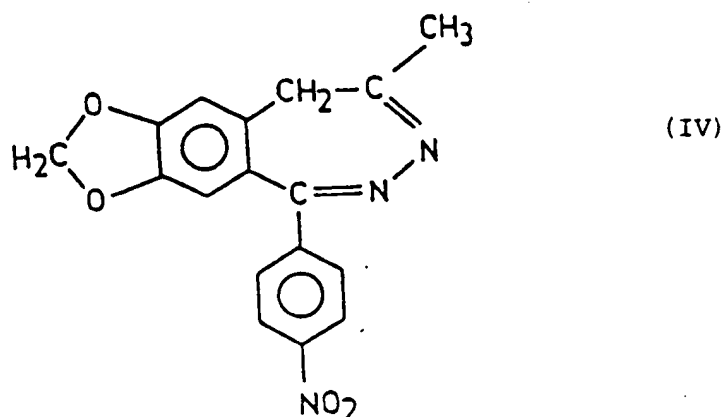
worin im Falle von  $\alpha$ -Aminosäuren  $R^5$  für Wasserstoffatom oder eine  $C_{1-4}$  Alkylgruppe steht und  $n$  1 ist, wogegen im Falle von  $\beta$ - $\epsilon$ -Aminosäuren  $R^5$  für Wasserstoffatom steht und  $n$  eine ganze Zahl von 2 bis 5 ist, acyliert wird, und gewünschtenfalls die Phthaloylgruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^2$  und die gestrichelten Linien die oben definierten Bedeutungen haben,  $R^3$  Wasserstoff bedeutet,  $R^4$  für eine durch eine Amino- oder Phthalimidogruppe substituierte  $C_{1-6}$  aliphatische Acylgruppe steht, sowohl  $R$  als auch  $R^1$  abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist; oder

d) eine Verbindung der allgemeinen Formel (III), worin  $R^4$  wie oben definiert ist, mit einer N-Phthaloylamino-säure der allgemeinen Formel (VI) acyliert wird, worin im Falle von  $\alpha$ -Aminosäuren  $R^5$  für Wasserstoffatom oder eine  $C_{1-4}$  Alkylgruppe steht und  $n$  1 ist, wogegen im Falle von  $\beta$ - $\epsilon$ -Aminosäuren  $R^5$  Wasserstoff bedeutet und  $n$  eine ganze Zahl von 2 bis 5 ist, und gewünschtenfalls die Phthaloylgruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^1$ ,  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  mit der Ausnahme von Wasserstoff wie oben definiert ist,  $R$  für eine durch eine Amino- oder Phthalimidogruppe substituierte  $C_{1-6}$  aliphatische Acylgruppe steht, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

e) eine Verbindung der Formel (II) mit einem  $C_{1-5}$  Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  eine  $C_{1-5}$  Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet,  $R$  und  $R^1$  abwesend sind, und zwischen den N(3) und C(4) Atomen eine Doppelbindung anwesend ist; oder

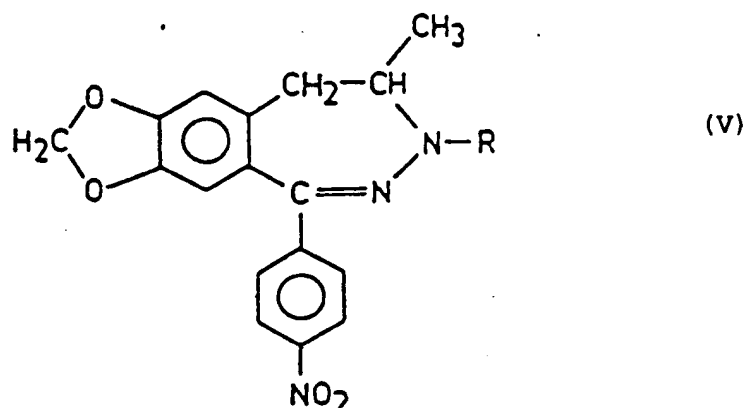
f) eine Verbindung der allgemeinen Formel (III), worin  $R^4$  wie oben definiert ist, mit einem  $C_{1-5}$  Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin  $R^1$  und  $R^2$  und die gestrichelten Linien wie oben definiert sind,  $R^3$  Wasserstoff bedeutet,  $R^4$  mit der Ausnahme von Wasserstoff wie oben definiert ist,  $R$  eine  $C_{1-5}$  Alkylcarbamoyl- oder Phenylcarbamoylgruppe steht, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

g) eine Verbindung der allgemeinen Formel (IV)



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selektiv zu einer neuen Verbindung der allgemeinen Formel (V)





20 reduziert wird, worin R Wasserstoff bedeutet, dann entweder die derart erhaltene Verbindung der allgemeinen Formel (V) durch Verwendung einer der obigen Verfahren b), d) oder f) acyliert und die Nitrogruppe der derart erhaltenen neuen Verbindung der allgemeinen Formel (V), worin R wie oben definiert ist, zu einer Amino-

25 gruppe reduziert wird, oder zuerst die Nitrogruppe reduziert und dann die derart erhaltene Verbindung der allgemeinen Formel (III), worin R<sup>4</sup> für Wasserstoff steht, acyliert durch Verwendung einer der obigen Verfahren b), d) oder f), um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>3</sup>, und R<sup>4</sup> Wasserstoff

30 bedeuten, R<sup>2</sup>, R und die gestrichelten Linien wie oben definiert sind, und zwischen den N(3) und C(4) Atome keine Doppelbindung anwesend ist; oder

h) eine neue Verbindung der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einer C<sub>1-6</sub> aliphatischen Carbonsäure, die gegebenenfalls durch eine Methoxy- Cyano-

35 oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder mit Benzoesäure oder mit einem reaktionsfähigen Derivat davon acyliert wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> und die gestrichelten Linien wie oben definiert sind, R und R<sup>4</sup> eine C<sub>1-6</sub> aliphatische

40 Acylgruppe bedeuten, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder eine Benzoylgruppe steht; R<sup>3</sup> für Wasserstoff steht; R<sup>4</sup> eine C<sub>1-5</sub> Alkylcarbonyl- oder Phenylcarbonylgruppe bedeutet; und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

i) eine neue Verbindung der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einem C<sub>1-5</sub> Alkylisocyanat oder Phenylisocyanat umgesetzt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R für eine

45 C<sub>1-6</sub> aliphatische Acylgruppe steht, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder eine Benzoylgruppe steht; R<sup>3</sup> für Wasserstoff steht; R<sup>4</sup> eine C<sub>1-5</sub> Alkylcarbonyl- oder Phenylcarbonylgruppe bedeutet; und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist; oder

j) eine neue Verbindung der allgemeinen Formel (I), worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R<sup>3</sup> und R<sup>4</sup> Wasserstoff bedeuten, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist, mit einer N-Phthaloylaminosäure der allgemeinen Formel (VI), worin im Falle von α-Aminosäuren R<sup>5</sup> für Wasserstoff oder eine C<sub>1-4</sub> Alkylgruppe steht und n 1 ist, wogegen im Falle von β-ε-Aminosäuren R<sup>5</sup> Wasserstoff bedeutet und n eine ganze Zahl vom 2 bis 5 ist, acyliert wird, und gewünschtenfalls die Phthaloyl-

50 gruppe entfernt wird, um Verbindungen der allgemeinen Formel (I) zu erhalten, worin R<sup>1</sup>, R<sup>2</sup> und die gestrichelten Linien wie oben definiert sind, R eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die gegebenenfalls durch eine Methoxy-, Cyano- oder Carboxylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder R eine Benzoylgruppe bedeutet; R<sup>3</sup> für Wasserstoff steht, R<sup>4</sup> eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die durch eine Amino- oder Phthalimidogruppe substituiert ist, und zwischen den N(3) und C(4) Atomen keine Doppelbindung anwesend ist,

55 und gewünschtenfalls eine Base der allgemeinen Formel (I), die durch eines der obigen Verfahren a) bis j) erhalten wurde, in ein Säureadditionssalz umgestaltet wird.

2. Verfahren nach Patentanspruch 1, Verfahren a) oder b), dadurch gekennzeichnet, dass die Acylierung in einem

entsprechenden Lösungsmittel, vorzugsweise Dichlormethan, mit einer Carbonsäure in der Anwesenheit von Dicyclohexylcarbodiimid bei einer Temperatur zwischen 10 und 30 °C durchgeführt wird.

3. Verfahren nach Patentanspruch 1, Verfahren a) oder b), dadurch gekennzeichnet, dass die Acylierung in Gegenwart oder Abwesenheit eines Lösungsmittels, durch Verwendung eines Carbonsäureanhydrids, gemischten Anhydrids oder Acylchlorids, gegebenenfalls in Gegenwart eines Säurebindemittels, bei einer Temperatur zwischen 0 °C und 150 °C durchgeführt wird.
4. Verfahren nach Patentanspruch 3, dadurch gekennzeichnet, dass die Reaktion in Chloroform oder Dichlormethan durchgeführt wird.
5. Verfahren nach Patentanspruch 1, Verfahren e) oder f), dadurch gekennzeichnet, dass die additive Acylierung durch Verwendung eines entsprechenden Alkyl- oder Phenylisocyanates in Dimethylformamid, Benzol oder Dichlormethan bei einer Temperatur zwischen 15 °C und 100 °C durchgeführt wird.
6. Verfahren nach Patentanspruch 1, Verfahren g), dadurch gekennzeichnet, dass die selektive Reduktion der Nitroverbindung der Formel (IV) durch Verwendung von Natriumborhydrid in einer Lösung eines C<sub>1-5</sub> aliphatischen Alkohols durchgeführt wird.
7. Verfahren nach Patentanspruch 1, Verfahren g) oder Patentanspruch 3, dadurch gekennzeichnet, dass die Reduktion der Nitrogruppe einer Verbindung der allgemeinen Formel (V) in einem methanolischen Medium, durch Verwendung von Hydrazin oder Hydrazinhydrat, in Gegenwart von Raney-Nickel oder Palladium als Katalysator bei einer Temperatur zwischen 10 °C und 65 °C durchgeführt wird.
8. Verfahren nach einem der Patentansprüche 1 bis 7 zur Herstellung von Verbindungen, dadurch gekennzeichnet, dass eine aus der folgenden Gruppe gewählte Verbindung hergestellt wird:  

1-(4-Aminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Aminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Acetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Propionylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Acetylaminophenyl)-3-propionyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Propionylaminophenyl)-3-formyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Trifluoracetylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-(4-Glycylaminophenyl)-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin hydrochlorid,  
N<sup>1</sup>-[4-(3-Acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin-1-yl)-phenyl]-N<sup>3</sup>-methylcarbamid,  
1-[4-(N,N-Dimethylglycylamino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-[4-(N,N-diethylglycylamino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin,  
1-[4-(1-Pyrrolidinoacetyl-amino)-phenyl]-3-acetyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin und sein Wasserstoff-fumarat und  
1-(4-Glycylaminophenyl)-3-methyl-carbamoyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepin.
9. Verfahren zur Herstellung einer pharmazeutischen Komposition, die als Wirkstoff ein neues N-Acyl-2,3-benzodiazepin-Derivat der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie im Patentanspruch 1 definiert sind, oder ein pharmazeutisch annehmbares Säureadditionssalz davon vermischt mit in der pharmazeutischen Industrie allgemein verwendeten Trägerstoffen und/oder Zusatzstoffen enthält, dadurch gekennzeichnet, dass als Wirkstoff ein neues N-Acyl-2,3-benzodiazepin-Derivat der allgemeinen Formel (I), worin R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> und die gestrichelten Linien wie im Patentanspruch definiert sind, oder ein pharmazeutisch annehmbares Säureadditionssalz davon, hergestellt durch Verwendung einer der im Patentanspruch 1 beanspruchten, Verfahrensvarianten a) bis j), mit in der pharmazeutischen Industrie allgemein verwendeten Trägerstoffen und/oder Zusatzstoffen vermischt und in eine pharmazeutische Komposition übergeführt werden.
10. Verfahren nach Patentanspruch 9, dadurch gekennzeichnet, dass Kompositionen, die zur Blockierung von einem oder mehreren stimulierenden Aminosäure-Rezeptoren in Säugetieren, die verminderte stimulierende Amino-

säure-Neurotransmission brauchen, oder zur Behandlung von Epilepsie in Säugetieren, oder für die Behandlung von Spasmen der skeletalen Muskulatur in Säugetieren durch Muskelrelaxation oder zur Behandlung von Gehirnschämie (Stroke) in Säugetieren geeignet sind, hergestellt werden.

11. Verfahren zur Herstellung von N-Acyl-2,3-benzodiazepin-Derivaten der allgemeinen Formel (V) wie im Patentanspruch 1 gegeben, worin

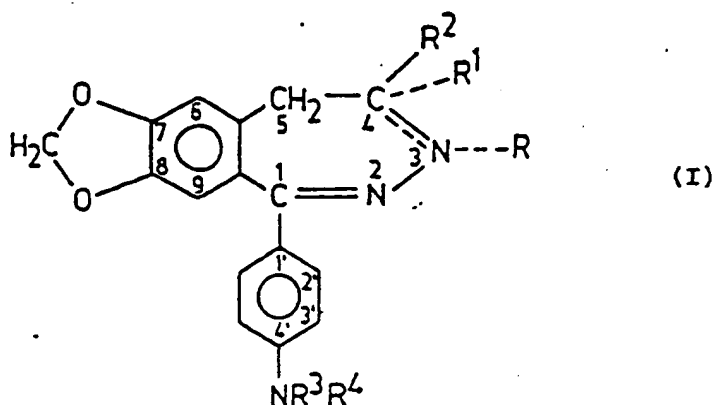
R Wasserstoff oder eine C<sub>1-6</sub> aliphatische Acylgruppe bedeutet, die gegebenenfalls durch eine Methoxy-, Cyano-, Carboxyl-, Amino-, C<sub>1-4</sub> Alkylamino-, Di(C<sub>1-4</sub> alkyl)-amino, Pyrrolidino-, Phthalimido- oder Phenylgruppe oder durch ein oder mehrere Halogenatom(e) substituiert ist; oder R eine Benzoyl-, Cyclopropancarbonyl-, C<sub>1-4</sub> Alkylcarbamoyl- oder Phenylcarbamoylgruppe bedeutet,

dadurch gekennzeichnet, dass eine Nitroverbindung der Formel (IV) selektiv reduziert wird.

# Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Dérivés de N-acyl-2,3-benzodiazépine de formule générale(I),



dans laquelle

R signifie un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou par un ou plusieurs atomes d'halogène; ou bien

R est un groupe benzoyle, cyclopropancarbonyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle; ou bien

R est absent, lorsqu'il existe entre les atomes N(3) et C(4) une double liaison;

R<sup>1</sup> est un atome d'hydrogène; ou

R<sup>1</sup> est absent, lorsqu'il existe entre les atomes N(3) et C(4) une double liaison;

R<sup>2</sup> signifie un groupe alkyle en C<sub>1-3</sub>; ou

R<sup>1</sup> et R<sup>2</sup> représentent ensemble un groupe méthylène et entre les atomes N(3) et C(4) il n'existe pas de double liaison;

R<sup>3</sup> signifie un atome d'hydrogène ou un groupe acyle aliphatique en C<sub>1-4</sub>;

R<sup>4</sup> représente un atome d'hydrogène; un groupe acyle aliphatique en C<sub>1-6</sub>,

éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle ou par un ou plusieurs atome(s) d'halogène;

ainsi qu'un groupe benzoyle, palmitoyle, cyclopropancarbonyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle;

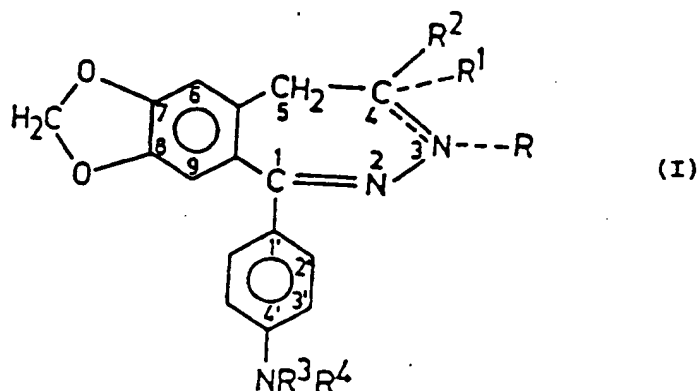
et les lignes en pointillé représentent des liaisons de valence éventuellement présentes, avec cette restriction qu'il n'existe pas de double liaison entre les atomes N(3) et C(4), lorsque R<sup>3</sup> aussi bien que R<sup>4</sup> signifie des atomes d'hydrogène, ainsi que leurs stéréo-isomères et les sels d'addition acide(là où c'est possible) de ces composés.

2. Un composé choisi dans le groupe qui contient les composés suivants:

1-(4-aminophényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-aminophényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-acétylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-acétylamino-phényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-formyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-trifluoracétylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 hydrochlorure de 1-(4-glycylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 N<sup>1</sup>-[4-(3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine-1-yl)-phényl]-N<sup>3</sup>-méthylcarbamide,  
 1-[4-(N,N-diméthylglycylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-[4-(N,N-diéthylglycylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-[4-(1-pyrrolidinoacétylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine et son fumarate d'hydrogène et de la  
 1-(4-glycylamino-phényl)-3-méthyl-carbamoyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine.

3. Une composition pharmaceutique qui contient à titre d'ingrédient actif un nouveau dérivé de N-acyl-2,3-benzodiazépine de formule générale (I), dans laquelle R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et les lignes en pointillé sont définis comme dans la revendication 1, ou un sel d'addition acide de celui-ci acceptable du point de vue pharmaceutique, mélangé à des porteurs et/ou des additifs généralement utilisés dans l'industrie pharmaceutique.

4. Procédé pour préparer de nouveaux dérivés de N-acyl-2,3-benzodiazépine de formule générale (I),



dans laquelle

R représente un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou bien par un ou plusieurs atome(s) d'halogène; ou R signifie un groupe benzoyle, cyclopropancarbonyle, alkylcarba-

moyle en C<sub>1-5</sub> ou phénylcarbamoyle; ou bien R est absent, lorsqu'entre les atomes N(3) et C(4) il existe une double liaison; R<sup>1</sup> signifie un atome d'hydrogène; ou R<sup>1</sup> est absent, lorsqu'entre les atomes N(3) et C(4) il existe une double liaison;

R<sup>2</sup> signifie un groupe alkyle en C<sub>1-3</sub>; ou

R<sup>1</sup> et R<sup>2</sup> représentent ensemble un groupe méthylène et entre les atomes N(3) et C(4) il n'existe pas de double liaison;

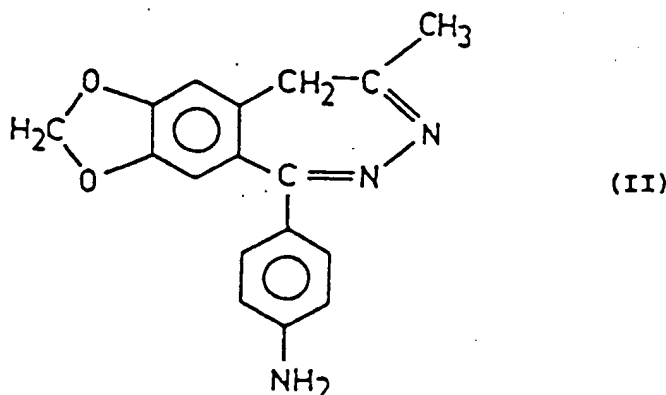
R<sup>3</sup> signifie un atome d'hydrogène ou un groupe acyle aliphatique en C<sub>1-4</sub>;

R<sup>4</sup> représente un atome d'hydrogène; un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>.

di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou par un ou plusieurs atome(s) d'halogène; ainsi que R<sup>4</sup> signifie un groupe benzoyle, palmitoyle, cyclopropanecarbonyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle; et

les lignes en pointillé signifient des liaisons de valence éventuellement présentes avec cette restriction qu'entre les atomes N(3) et C(4) il n'existe pas de double liaison, lorsqu'aussi bien R<sup>3</sup> que R<sup>4</sup> signifient un atome d'hydrogène, et leurs stéréo-isomères ainsi que leurs sels d'addition acide, caractérisé en ce que

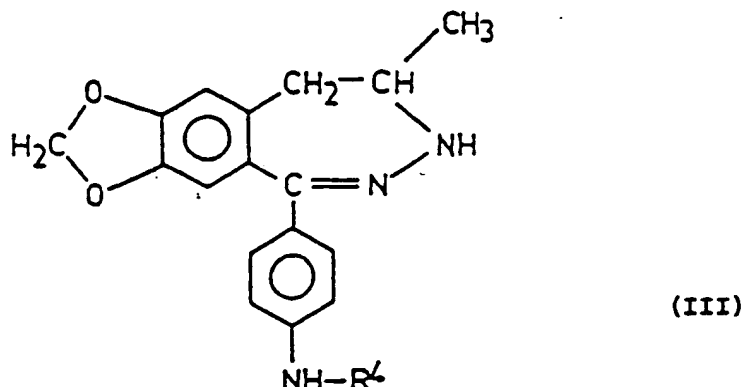
a) un composé de formule (II)



avec un acide carboxylique aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle ou phényle ou par un ou plusieurs atome(s) d'halogène; ou avec de l'acide benzoïque, cyclopropane-carboxylique ou palmitinique ou avec un dérivé réactif de ceux-ci; et, si cela est désiré, en faisant réagir un nouveau composé ainsi obtenu de formule générale (I), dans laquelle R<sup>4</sup> représente un groupe acyle aliphatique en C<sub>1-6</sub> substitué par un atome d'halogène, avec une alkylamine en C<sub>1-4</sub>, une di(alkyl en C<sub>1-4</sub>)amine ou une pyrrolidine, afin d'obtenir des composés de formule générale (I)

dans laquelle R<sup>2</sup>, R<sup>3</sup> et les lignes en pointillé sont définis comme ci-dessus, R<sup>4</sup> signifie un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, phényle, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino ou pyrrolidino, ou un ou plusieurs atome(s) d'halogène; ou un groupe benzoyle, cyclopropanecarbonyle ou palmitoyle; R et R<sup>1</sup> sont absents, et entre les atomes N(3) et C(4) il existe une double liaison;

b) on acyle un composé de formule générale (III),



dans laquelle

$R^4$  est défini comme ci-dessus, avec un acide carboxylique aliphatique en  $C_{1-6}$  éventuellement substitué par un groupe méthoxy, cyano, carboxyle ou phényle, ou par un ou plusieurs atome(s) d'halogène; ou avec de l'acide benzoïque ou

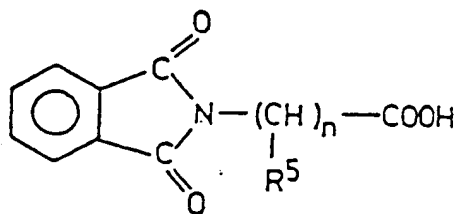
cyclopropanecarboxylique ou avec un dérivé réactif de ceux-ci; et, si cela est désiré, en faisant réagir un nouveau composé ainsi obtenu de formule générale (I), dans laquelle  $R^4$  signifie un groupe acyle aliphatique en  $C_{1-6}$  substitué par un atome d'halogène, avec une alkylamine en  $C_{1-4}$ , une di(alkyl en  $C_{1-4}$ )amine ou une pyrrolidine, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  et les lignes en pointillé sont

définis comme ci-dessus, R représente un groupe acyle aliphatique en  $C_{1-6}$ , éventuellement substitué par un groupe méthoxy, cyano, carboxyle, phényle, alkylamino en  $C_{1-4}$ , di(alkyl en  $C_{1-4}$ )amino ou pyrrolidino, ou par un ou plusieurs atome(s) d'halogène;

ou un groupe benzoyle ou cyclopropanecarbonyle; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

c) on acyle un composé de formule (II) avec un acide N-phthaloylaminé de formule générale (VI),

(VI)



dans laquelle  $R^5$  représente un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  et n signifie 1 en cas d'acides  $\alpha$ -aminés, tandis que  $R^5$  signifie un atome d'hydrogène et n signifie un nombre entier de 2 à 5 en cas d'acides  $\beta$ -aminés, et, si cela est désiré, on enlève le groupe phthaloyle afin d'obtenir des composés de formule générale (I),

dans laquelle  $R^2$  et les lignes en pointillé sont comme définis ci-dessus,  $R^3$  signifie un atome d'hydrogène,  $R^4$  signifie un groupe acyle aliphatique en  $C_{1-6}$ , substitué par un groupe amino ou phthalimido, aussi bien R que  $R^1$  sont absents, et il existe une double liaison entre les atomes N(3) et C(4); ou

d) on acyle un composé de formule générale (III), dans laquelle  $R^4$  est défini comme ci-dessus, avec de l'acide N-phthaloyl-aminé de formule générale (VI), dans laquelle en cas d'acides  $\alpha$ -aminés  $R^5$  représente un atome d'hydrogène ou un group alkyle en  $C_{1-4}$  et n est égal à 1, tandis qu'en cas d'acides  $\beta$ -aminés  $R^5$  signifie un atome d'hydrogène et n est un nombre entier de 2 à 5,

et si cela est désiré, on enlève le groupe phthaloyle, afin d'obtenir des composés de formule générale

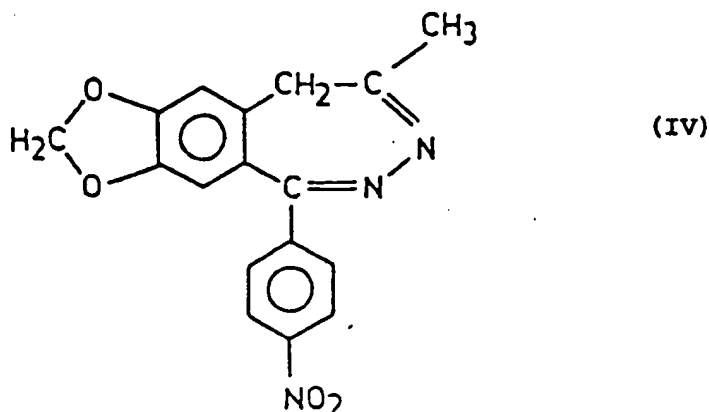
(I), dans laquelle  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,  $R^3$  signifie un atome d'hydrogène,  $R^4$  est défini comme ci-dessus à l'exception de l'hydrogène, R représente un group acyle aliphatique en  $C_{1-6}$  substitué par un gr upe amino ou phthalimido, et entre les atomes N(3) et C(4) il n'existe pas de doubl  
liaison; ou

e) on fait réagir un composé de formule (II) avec un isocyanate d'alkyle en  $C_{1-5}$  ou avec un isocyanate de phé-  
nyle, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^2$  et les lignes en pointillé sont définis  
comme ci-dessus,  $R^3$  signifie un atome d'hydrogène,  $R^4$  représente un groupe alkylcarbamoyle ou phénylcar-  
bamoyle en  $C_{1-5}$ , R et  $R^1$  sont absents, et entre les atomes N(3) et C(4) il existe une double liaison; ou

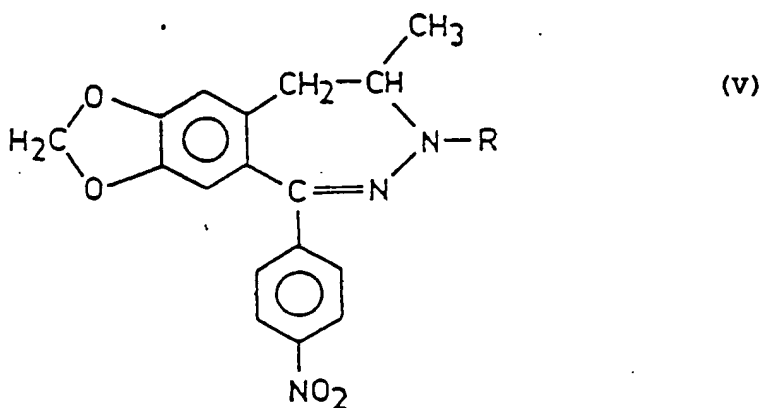
f) on fait réagir un composé de formule générale (III), dans laquelle  $R^4$  est défini comme ci-dessus, avec un  
isocyanate d'alkyle en  $C_{1-5}$  ou un isocyanate de phényle afin d'obtenir des composés de formule générale (I),  
dans laquelle  $R^1$  et  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,  $R^3$  représente un atome d'hydro-  
gène,  $R^4$  est défini comme ci-dessus à l'exception de l'hydrogène, R représente un groupe alkylcarbamoyle ou  
phénylcarbamoyle en  $C_{1-5}$ , et entre les atomes N(3) et C(4) il n'existe pas de double liaison;

ou

g) on réduit de manière sélective un composé de formule générale (IV)



en un nouveau composé de formule générale (V)



dans laquelle R représente un atome d'hydrogène, ensuite ou bien on acyle un composé ainsi obtenu  
de formule générale (V) par l'application d'un des procédés ci-dessus b), d) ou f) et on réduit le groupe nitro du

nouveau composé ainsi obtenu de formule générale (V),

dans laquelle R est défini comme ci-dessus, en un groupe amino, ou bien on réduit d'abord le groupe nitré et ensuite on acyle le composé ainsi obtenu de formule générale (III), dans laquelle R<sup>4</sup> représente un atome d'hydrogène, par l'application d'un des procédés b), d) ou f), afin d'obtenir des composés de formule générale (I), dans laquelle R<sup>1</sup>, R<sup>3</sup>, et R<sup>4</sup> signifient un atome d'hydrogène, R<sup>2</sup>, R et les lignes en pointillé sont définies comme ci-dessus, et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

h) on acyle un nouveau composé de formule générale (I), dans laquelle

R, R<sup>1</sup>, R<sup>2</sup> et les lignes en pointillé sont définies comme ci-dessus,

R<sup>3</sup> et R<sup>4</sup> signifient un atome d'hydrogène, et entre les

atomes N(3) et C(4) il n'existe pas de double liaison, avec un acide carboxylique aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou avec un acide benzoïque; ou avec un dérivé réactif de celui-ci, afin d'obtenir des composés de formule générale (I), dans laquelle

R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> et les lignes en pointillé sont définies comme ci-dessus, R et R<sup>4</sup> signifient un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou un groupe benzoylé; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

on fait réagir un nouveau composé de formule générale (I), dans laquelle

R, R<sup>1</sup>, R<sup>2</sup> et les lignes en pointillé sont définies comme ci-dessus, R<sup>3</sup> et R<sup>4</sup> signifient un atome d'hydrogène, et entre les atomes

N(3) et C(4) il n'existe pas de double liaison, avec un isocyanate d'alkyle en C<sub>1-5</sub> ou un isocyanate de phényle, afin d'obtenir des composés de formule générale (I), dans laquelle R<sup>1</sup>, R<sup>2</sup> et les lignes en pointillé sont définies comme ci-dessus, R représente un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou un groupe benzoylé; R<sup>3</sup> représente un atome d'hydrogène; R<sup>4</sup> signifie un groupe alkylcarbamoylé en C<sub>1-5</sub> ou un groupe phénylcarbamoylé; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

j) on acyle un nouveau composé de formule générale (I), dans laquelle

R<sup>1</sup>, R<sup>2</sup> et les lignes en pointillé sont définies comme ci-dessus, R<sup>3</sup> et R<sup>4</sup> signifient un atome d'hydrogène, et entre les atomes

N(3) et C(4) il n'existe pas de double liaison,

avec un acide N-phthaloylaminé de formule générale (VI), dans laquelle en cas d'acides  $\alpha$ -aminés R<sup>5</sup> représente un atome d'hydrogène ou un groupe alkyle en C<sub>1-4</sub> et n est égal à 1, et en cas d'acides  $\beta$ - $\epsilon$ -aminés R<sup>5</sup> signifie un atome d'hydrogène et n est un nombre entier de 2 à 5, et si cela est désiré, on enlève le groupe phthaloylé, afin d'obtenir des composés de formule générale

(I), dans laquelle R<sup>1</sup>, R<sup>2</sup> et les lignes en pointillé sont définies comme ci-dessus, et R représente un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou un groupe benzoylé; R<sup>3</sup> représente un atome d'hydrogène, R<sup>4</sup> représente un groupe acyle aliphatique en C<sub>1-6</sub>, substitué par un groupe amino ou phthalimido, et entre les atomes N(3) et C(4) il n'existe pas de double liaison,

et si cela est désiré, on convertit une base de formule générale (I),

obtenue par l'un quelconque des procédés a) à j), en un sel d'addition acide.

5. Procédé selon la revendication 4, procédé a) ou b), caractérisé en ce que l'on effectue l'acylation dans un solvant convenable, de préférence dans du dichlorométhane, avec un acide carboxylique en la présence de dicyclohexylcarbodiimide à une température comprise entre 10 et 30 °C.
6. Procédé selon la revendication 4, procédé a) ou b), caractérisé en ce que l'on effectue l'acylation en la présence ou en l'absence d'un solvant, en mettant en oeuvre de l'anhydride d'acide carboxylique, de l'anhydride ou du chlorure d'acyle mélangés, éventuellement en la présence d'un agent liant les acides à une température comprise entre 0 °C et 150 °C.
7. Procédé selon la revendication 6, caractérisé en ce que l'on effectue la réaction dans du chloroforme ou du dichlorométhane.
8. Procédé selon la revendication 4, procédé e) ou f), caractérisé en ce que l'on effectue l'acylation additive en mettant en oeuvre un isocyanate d'alkyle ou de phényle convenable dans du diméthylformamide, dans du benzène ou



du dichlorométhane à une température comprise entre 15 C et 100 C .

9. Procédé selon la revendication 4, procédé g), caractérisé en ce que l'on effectue la réduction sélective du composé nitro de formule (IV) en mettant en oeuvre du borohydrure de sodium dans une solution d'alcool aliphatique en C<sub>1</sub>.

10. Procédé selon la revendication 4, procédé g) ou revendication 6, caractérisé en ce que l'on effectue la réduction du groupe nitro du composé de formule générale (v) dans un milieu méthanolique, en mettant en oeuvre de l'hydrazine ou de l'hydrate d'hydrazine, en la présence de nickel Raney ou de palladium à titre de catalyseur à une température comprise entre 10 C et 65 C .

11. Procédé pour préparer du composé pharmaceutique selon la revendication 3, caractérisé en ce que l'on ajoute à titre d'ingrédient actif un nouveau dérivé de N-acyl-2,3-benzodiazépine de formule générale(I), dans laquelle R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et les lignes en pointillé sont définis comme dans la revendication 1, ou un sel d'addition acide de ceux-ci acceptable du point de vue pharmaceutique, avec des porteurs et/ou additifs généralement mis en oeuvre dans l'industrie pharmaceutique, et l'on les convertit en une composition pharmaceutique.

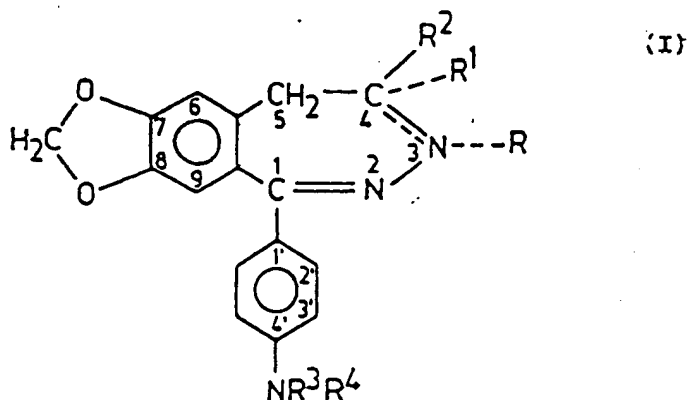
12. Mise en oeuvre des composés préparés selon les revendications 1 à 8, pour préparer des médicaments, en particulier ceux bloquant un ou plusieurs récepteurs excitateurs d'acide aminé chez des mammifères ayant besoin d'une diminution de la neurotransmission excitatrice d'acide aminé, ou ceux aptes à traiter l'épilepsie chez les mammifères, ou ceux aptes à traiter les spasmes de la musculature squelettique chez les mammifères par la relaxation musculaire ou à traiter l'ischémie cérébrale (stroke) chez les mammifères.

13. Dérivés de N-acyl-2,3-benzodiazépine de formule générale (V) comme décrits dans la revendication 4, dans laquelle

R représente un atome d'hydrogène ou un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou par un ou plusieurs atome(s) d'halogène; ou R représente un groupe benzoyle, cyclopropancarboxyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle.

# Revendications pour les Etats contractants suivants : GR, ES

1. Procédé pour préparer de nouveaux dérivés de N-acyl-2,3-benzodiazépine de formule générale (I),

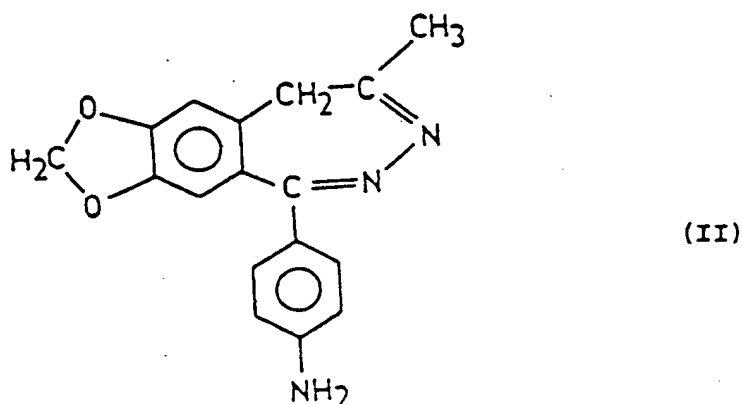


dans laquelle

R représente un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou bien par un ou plusieurs atome(s) d'halogène; ou R signifie un groupe benzoyle, cyclopropancarboxyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle; ou bien R est absent, lorsqu'entre les atomes N(3) et C(4) il existe une double liaison;

- R<sup>1</sup> signifie un atome d'hydrogène; ou R<sup>1</sup> est absent, lorsqu'entre les atomes N(3) et C(4) il existe une double liaison;
- R<sup>2</sup> signifie un groupe alkyle en C<sub>1-3</sub>; ou
- R<sup>1</sup> et R<sup>2</sup> représentent ensemble un groupe méthylène et entre les atomes N(3) et C(4) il n'existe pas de double liaison;
- R<sup>3</sup> signifie un atome d'hydrogène ou un groupe acyle aliphatique en C<sub>1-4</sub>;
- R<sup>4</sup> représente un atome d'hydrogène; un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou par un ou plusieurs atome(s) d'halogène; ainsi que R<sup>4</sup> signifie un groupe benzoyle, palmitoyle, cyclopropanecarboxyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle; et les lignes en pointillé signifient des liaisons de valence éventuellement présentes avec cette restriction qu'entre les atomes N(3) et C(4) il n'existe pas de double liaison, lorsqu'aussi bien R<sup>3</sup> que R<sup>4</sup> signifient un atome d'hydrogène, et leurs stéréo-isomères ainsi que leurs sels d'addition acide, caractérisé en ce que

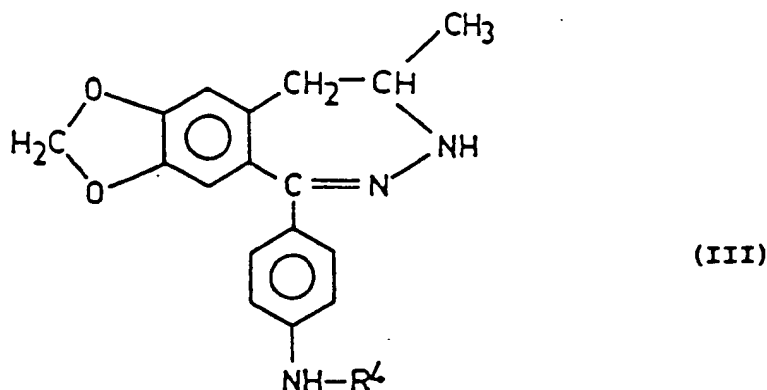
a) un composé de formule (II)



avec un acide carboxylique aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle ou phényle ou par un ou plusieurs atome(s) d'halogène; ou avec de l'acide benzoïque, cyclopropane-carboxylique ou palmitinique ou avec un dérivé réactif de ceux-ci; et, si cela est désiré, en faisant réagir un nouveau composé ainsi obtenu de formule générale (I), dans laquelle R<sup>4</sup> représente un groupe acyle aliphatique en C<sub>1-6</sub> substitué par un atome d'halogène, avec une alkylamine en C<sub>1-4</sub>, une di(alkyl en C<sub>1-4</sub>)amine ou une pyrrolidine, afin d'obtenir des composés de formule générale (I)

dans laquelle R<sup>2</sup>, R<sup>3</sup> et les lignes en pointillé sont définies comme ci-dessus, R<sup>4</sup> signifie un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, phényle, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino ou pyrrolidino, ou un ou plusieurs atome(s) d'halogène; ou un groupe benzoyle, cyclopropanecarboxyle ou palmitoyle; R et R<sup>1</sup> sont absents, et entre les atomes N(3) et C(4) il existe une double liaison;

b) on acyle un composé de formule générale (III),

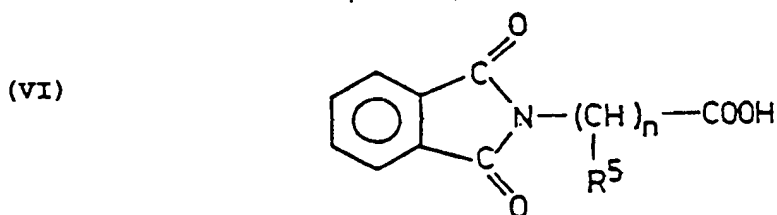


dans laquelle

$R^4$  est défini comme ci-dessus, avec un acide carboxylique aliphatique en  $C_{1-6}$  éventuellement substitué par un groupe méthoxy, cyano, carboxyle ou phényle, ou par un ou plusieurs atome(s) d'halogène; ou avec de l'acide benzoïque ou cyclopropanecarboxylique ou avec un dérivé réactif de ceux-ci; et, si cela est désiré, en faisant réagir un nouveau composé ainsi obtenu de formule générale (I), dans laquelle  $R^4$  signifie un groupe acyle aliphatique en  $C_{1-6}$  substitué par un atome d'halogène, avec une alkylamine en  $C_{1-4}$ , une di(alkyl en  $C_{1-4}$ )amine ou une pyrrolidine, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  et les lignes en pointillé sont définis comme ci-dessus, R représente un groupe acyle aliphatique en  $C_{1-6}$ , éventuellement substitué par un groupe méthoxy, cyano, carboxyle, phényle, alkylamino en  $C_{1-4}$ , di(alkyl en  $C_{1-4}$ )amino ou pyrrolidino, ou par un ou plusieurs atome(s) d'halogène;

ou un groupe benzoyle ou cyclopropanecarbonyle; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

c) on acyle un composé de formule (II) avec un acide N-phthaloylaminé de formule générale (VI),



dans laquelle  $R^5$  représente un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  et n signifie 1 en cas d'acides  $\alpha$ -aminés, tandis que  $R^5$  signifie un atome d'hydrogène et n signifie un nombre entier de 2 à 5 en cas d'acides  $\beta$ -aminés, et, si cela est désiré, on enlève le groupe phthaloyle afin d'obtenir des composés de formule générale (I),

dans laquelle  $R^2$  et les lignes en pointillé sont comme définis ci-dessus,  $R^3$  signifie un atome d'hydrogène,  $R^4$  signifie un groupe acyle aliphatique en  $C_{1-6}$ , substitué par un groupe amino ou phthalimido, aussi bien R que  $R^1$  sont absents, et il existe une double liaison entre les atomes N(3) et C(4); ou

d) on acyle un composé de formule générale (III), dans laquelle  $R^4$  est défini comme ci-dessus, avec de l'acide N-phthaloyl-aminé de formule générale (VI), dans laquelle en cas d'acides  $\alpha$ -aminés  $R^5$  représente un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  et n est égal à 1, tandis qu'en cas d'acides  $\beta$ -aminés  $R^5$  signifie un atome d'hydrogène et n est un nombre entier de 2 à 5,

et si cela est désiré, on enlève le groupe phthaloyle, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,  $R^3$  signifie un atome d'hydrogène,  $R^4$  est défini comme ci-dessus à l'exception de l'hydrogène, R représente un groupe acyle aliphatique

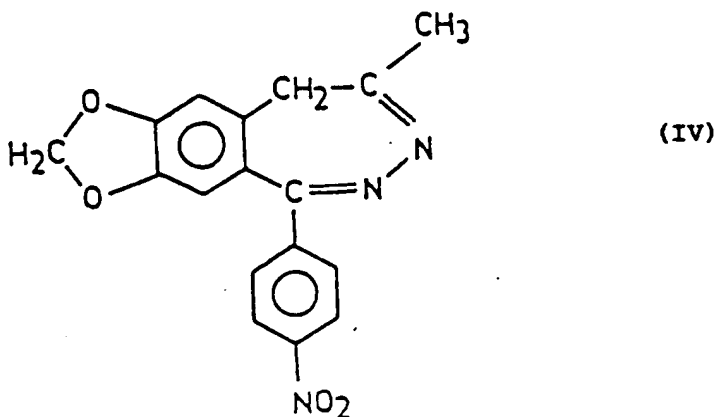
en C<sub>1-6</sub> substitué par un groupe amino ou phthalimido, et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

e) on fait réagir un composé de formule (II) avec un isocyanate d'alkyle en C<sub>1-5</sub> ou avec un isocyanate de phényle, afin d'obtenir des composés de formule générale (I), dans laquelle R<sup>2</sup> et les lignes en pointillé sont définis comme ci-dessus, R<sup>3</sup> signifie un atome d'hydrogène, R<sup>4</sup> représente un groupe alkylcarbamoyle ou phénylcarbamoyle en C<sub>1-5</sub>, R et R<sup>1</sup> sont absents, et entre les atomes N(3) et C(4) il existe une double liaison; ou

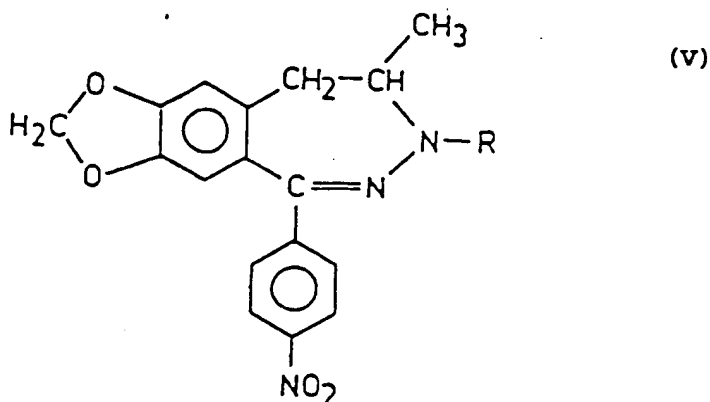
f) on fait réagir un composé de formule générale (III), dans laquelle est R<sup>4</sup> est défini comme ci-dessus, avec un isocyanate d'alkyle en C<sub>1-5</sub> ou un isocyanate de phényle afin d'obtenir des composés de formule générale (I), dans laquelle R<sup>1</sup> et R<sup>2</sup> et les lignes en pointillé sont définis comme ci-dessus, R<sup>3</sup> représente un atome d'hydrogène, R<sup>4</sup> est défini comme ci-dessus à l'exception de l'hydrogène, R représente un groupe alkylcarbamoyle ou phénylcarbamoyle en C<sub>1-5</sub>, et entre les atomes N(3) et C(4) il n'existe pas de double liaison;

ou

g) on réduit de manière sélective un composé de formule générale (IV)



en un nouveau composé de formule générale (V)



dans laquelle R représente un atome d'hydrogène, ensuite ou bien on acyle un composé ainsi obtenu de formule générale (V) par l'application d'un des procédés ci-dessus b), d) ou f), et on réduit le groupe nitro du nouveau composé ainsi obtenu de formule générale (V),

dans laquelle R est défini comme ci-dessus, en un groupe amino, ou bien on réduit d'abord le groupe nitro et ensuite on acyle le composé ainsi obtenu de formule générale (III), dans laquelle R<sup>4</sup> représente un

atome d'hydrogène, par l'application d'un des procédés b), d) ou f), afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$ , et  $R^4$  signifient un atome d'hydrogène,  $R^3$ , R et les lignes en pointillé sont définis comme ci-dessus, et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

h) on acyle un nouveau composé de formule générale (I), dans laquelle

$R$ ,  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,

$R^3$  et  $R^4$  signifient un atome d'hydrogène, et entre les atomes N(3) et C(4) il n'existe pas de double liaison, avec un acide carboxylique amphipatique en  $C_{1-6}$ , éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou avec un acide benzoïque; ou avec un dérivé réactif de celui-ci, afin d'obtenir des composés de formule générale (I), dans laquelle

$R^1$ ,  $R^2$  et  $R^3$  et les lignes en pointillé sont définis comme ci-dessus, R et  $R^4$  signifient un groupe acyle aliphatique en  $C_{1-6}$  éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atom(s) d'halogène; ou un groupe benzoyle; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou on fait réagir un nouveau composé de formule générale (I), dans laquelle

$R$ ,  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,  $R^3$  et  $R^4$  signifient un atome d'hydrogène, et entre les atomes N(3) et C(4) il n'existe pas de double liaison, avec un isocyanate d'alkyle en  $C_{1-5}$  ou un isocyanate de phényle, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus, R représente un groupe acyle aliphatique en  $C_{1-6}$ , éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou un groupe benzoyle;  $R^3$  représente un atome d'hydrogène;  $R^4$  signifie un groupe alkylcarbamoyle en  $C_{1-5}$  ou un groupe phénylcarbamoyle; et entre les atomes N(3) et C(4) il n'existe pas de double liaison; ou

j) on acyle un nouveau composé de formule générale (I), dans laquelle

$R^1$ ,  $R^2$  et les lignes en pointillé sont définis comme ci-dessus,  $R^3$  et  $R^4$  signifient un atome d'hydrogène, et entre les atomes N(3) et C(4) il n'existe pas de double liaison, avec un acide N-phthaloylaminé de formule générale (VI), dans laquelle en cas d'acides  $\alpha$ -aminés  $R^5$  représente un atome d'hydrogène ou un groupe alkyle en  $C_{1-4}$  et n est égal à 1, et en cas d'acides  $\beta$ - $\epsilon$ -aminés  $R^5$  signifie un atome d'hydrogène et n est un nombre entier de 2 à 5, et si cela est désiré, on enlève le groupe phthaloyle, afin d'obtenir des composés de formule générale (I), dans laquelle  $R^1$ ,  $R^2$  et les lignes en pointillé sont définis

comme ci-dessus, et R représente un groupe acyle aliphatique en  $C_{1-6}$ , éventuellement substitué par un groupe méthoxy, cyano ou carboxyle ou par un ou plusieurs atome(s) d'halogène; ou un groupe benzoyle;  $R^3$  représente un atome d'hydrogène,  $R^4$  représente un groupe acyle aliphatique en  $C_{1-6}$ , substitué par un groupe amino ou

phthalimido, et entre les atomes N(3) et C(4) il n'existe pas de double liaison, et si cela est désiré, on convertit une base de formule générale (I), obtenue par l'un quelconque des procédés a) à j), en un sel d'addition acide.

2. Procédé selon la revendication 1, procédé a) ou b), caractérisé en ce que l'on effectue l'acylation dans un solvant convenable, de préférence dans du dichlorométhane, avec un acide carboxylique en la présence de dicyclohexylcarbodiimide à une température comprise entre 10 et 30 C.
3. Procédé selon la revendication 1, procédé a) ou b), caractérisé en ce que l'on effectue l'acylation en la présence ou en l'absence d'un solvant, en mettant en oeuvre de l'anhydride d'acide carboxylique, de l'anhydride ou du chlorure d'acyle mélangés, éventuellement en la présence d'un agent liant les acides à une température comprise entre 0 C et 150 C.
4. Procédé selon la revendication 3, caractérisé en ce que l'on effectue la réaction dans du chloroforme ou du dichlorométhane.
5. Procédé selon la revendication 1, procédé e) ou f), caractérisé en ce que l'on effectue l'acylation additive en mettant en oeuvre un isocyanate d'alkyle ou de phényle convenable dans du diméthylformamide, dans du benzène ou du dichlorométhane à une température comprise entre 15 C et 100 C.
6. Procédé selon la revendication 1, procédé g), caractérisé en ce que l'on effectue la réduction sélective du composé nitro d formule (IV) en mettant en oeuvre du borohydrure de sodium dans une solution d'alcool aliphatique en  $C_1$ .

7. Procédé selon la revendication 1, procédé g) ou revendication 3, caractérisé en ce que l'on effectue la réduction du groupe nitro du composé de formule générale (V) dans un milieu méthanolique, en mettant en oeuvre de l'hydrazine ou de l'hydrat d'hydrazine, en la présence de nickel Raney ou de palladium à titre de catalyseur à une température comprise entre 10 C et 65 C.

8. Un composé selon l'une quelconque des revendications 1 à 7, caractérisé en ce que l'on prépare un composé choisi dans le groupe comprenant les composés suivants:

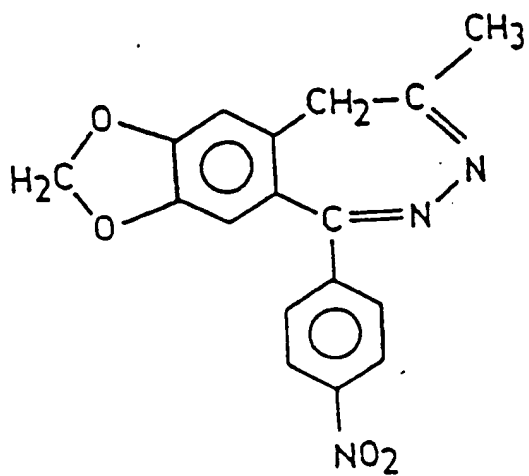
1-(4-aminophényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-aminophényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-acétylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylène-dioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-acétylamino-phényl)-3-propionyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-propionylamino-phényl)-3-formyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-(4-trifluoracétylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 hydrochlorure de 1-(4-glycylamino-phényl)-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 N<sup>1</sup>-[4-(3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine-1-yl)-phényl]-N3-méthylcarbamide,  
 1-[4-(N,N-Diméthylglycylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-[4-(N,N-diéthylglycylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine,  
 1-[4-(1-pyrrolidinoacétylamino)-phényl]-3-acétyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine et son fumarate d'hydrogène et de la 1-(4-glycylamino-phényl)-3-méthyl-carbamoyl-4-méthyl-7,8-méthylènedioxy-3,4-dihydro-5H-2,3-benzodiazépine.

9. Procédé pour préparer une composition pharmaceutique contenant à titre d'ingrédient actif un nouveau dérivé de N-acyl-2,3-benzodiazépine de formule générale (I), dans laquelle R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et les lignes en pointillé sont définis comme dans la revendication 1, ou un sel d'addition acide de celui-ci acceptable du point de vue pharmaceutique mélangé à des porteurs et/ou additifs généralement utilisés dans l'industrie pharmaceutique, caractérisé en ce que l'on met en oeuvre à titre d'ingrédient actif un nouveau dérivé de N-acyl-2,3-benzodiazépine de formule générale(I), dans laquelle R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et les lignes en pointillé sont définis comme dans la revendication 1, ou un sel d'addition acide de celui-ci acceptable du point de vue pharmaceutique, mélangé à des porteurs et/ou additifs généralement utilisés dans l'industrie pharmaceutique, préparé par la mise en oeuvre de l'un quelconque des procédés a) à j) tels que revendiqués dans la revendication 1, avec des porteurs et/ou additifs généralement utilisés dans l'industrie pharmaceutique, et on les convertit en une composition pharmaceutique.

10. Procédé selon la revendication 9, caractérisé en ce que l'on prépare des compositions aptes à bloquer un ou plusieurs récepteurs excitateurs d'acide aminé chez des mammifères ayant besoin d'une diminution de la neurotransmission excitatrice d'acide aminé, ou ceux aptes à traiter l'épilepsie chez les mammifères, ou ceux aptes à traiter les spasmes de la musculature squelettique chez les mammifères par la relaxation musculaire ou à traiter l'ischémie cérébrale (stroke) chez les mammifères.

11. Procédé pour préparer des dérivés de N-acyl-2,3-benzodiazépine de formule générale (V) tels que définis dans la revendication 1, dans laquelle

R représente un atome d'hydrogène ou un groupe acyle aliphatique en C<sub>1-6</sub>, éventuellement substitué par un groupe méthoxy, cyano, carboxyle, amino, alkylamino en C<sub>1-4</sub>, di(alkyl en C<sub>1-4</sub>)amino, pyrrolidino, phthalimido ou phényle, ou par un ou plusieurs atome(s) d'halogène; ou R représente un groupe benzoyle, cyclopropancarboxyle, alkylcarbamoyle en C<sub>1-5</sub> ou phénylcarbamoyle, caractérisé en ce que l'on réduit de manière sélective un composé nitro de formule(IV)



(IV) .